Venous Thromboembolism and Risk of Recurrence

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ENGLISH SUMMARY

Venous thromboembolism is a common vascular disease affecting millions of individuals worldwide. Venous thromboembolism covers both deep vein thrombosis and pulmonary embolism. One major concern related to venous thromboembolism is a long-lasting high risk of recurrence, which is associated with high morbidity and mortality.

Anticoagulation is highly effective for preventing venous thromboembolism recurrence but involves a trade-off, since this treatment can also cause severe and potentially life-threatening bleeding. The optimal duration of anticoagulation is undetermined – in large due to uncertainties about the individual patient's risk of recurrence. International guidelines do not recommend any specific risk stratification tool to guide the treatment decision, besides an arbitrary categorisation into 'provoked', 'unprovoked' and 'cancer-related' venous thromboembolism. Furthermore, despite recommendations of anticoagulant treatment to all patients with incident venous thromboembolism, some patients never initiate this critical treatment.

This thesis is based on three register-based studies ultimately striving towards a more informed navigation in some of the dilemmas of venous thromboembolism treatment. Study 1 aimed at clarifying recurrence risk according to the categorization of venous thromboembolism suggested in most guidelines. After 10 years, the risk of recurrence was approximately 20% among patients with cancer and 'unprovoked' venous thromboembolism. However, contrary to common belief, patients with 'provoked' venous thromboembolism also carried a high recurrence risk greater than 15% after 10 years. Therefore, in Study 2 we abandoned the traditional arbitrary categorization of 'provoked' and 'unprovoked' venous thromboembolism, when we derived and internally validated sex-specific risk prediction scores for venous thromboembolism recurrence. We developed a well-calibrated risk score under the acronym AIM-SHA-RP, which may be used to guide decisions of oral anticoagulant treatment duration following incident VTE. Finally, to embolden focus on adherence and optimal treatment, Study 3 investigated potential predictors of non-initiation of anticoagulation after incident venous thromboembolism. Up to 24% did not initiate relevant anticoagulant treatment within 30 days after discharge. Most robust predictors of non-initiation were demographic and condition-related factors including female sex, young age, and incident deep venous thrombosis.

This Ph.D. dissertation emphasizes a continued need for improvement of venous thromboembolism treatment and management. The thesis clarifies that venous thromboembolism recurrence is common, and that many patients receive no or potentially sub-optimal anticoagulant treatment. Alongside with other scientific contributions, the presented studies may support the decision of anticoagulant treatment duration of the many patients suffering from venous thromboembolism.

DANSK RESUME

Blodprop i venerne, også kaldet venøs tromboemboli, dækker både over blodpropper i de dybe vener (dyb venetrombose) samt blodpropper i lungearterierne (lungeemboli). Venøs tromboemboli er en hyppig vaskulær sygdom, som hvert år rammer millioner af mennesker på verdensplan. En af hovedbekymringerne efter venøs tromboemboli er den høje risiko for efterfølgende ny (recidiv) blodprop i venerne. Recidiv af venøs tromboemboli er forbundet med både øget sygelighed og høj dødelighed.

Blodfortyndende medicin er yderst effektiv til at forebygge recidiv af venøs tromboemboli, men kan også kan forårsage svær og potentielt livstruende blødning. Den optimale varighed af behandling med blodfortyndende medicin er uafklaret – primært pga. usikkerhed omkring risikoen for recidiv-risikoen hos den enkelte patient. Internationale retningslinjer anbefaler ikke noget specifikt værktøj til opdeling af risikogrupper, som en guide for beslutningen af varighed af behandling udover en arbitrær opdeling i ”provokeret”, ”uprovokeret” og ”cancer-relateret” venøs tromboemboli. Til trods for, at blodfortyndende medicin anbefales til alle patienter med venøs tromboemboli, er der desuden patienter, der aldrig opstarter den relevante behandling.

Denne afhandling bygger på tre register-baserede studier, der bidrager med ny viden til dilemmaet omkring behandling af venøs tromboemboli. Formålet med Studie 1 var, at belyse risikoen for recidiv i forhold til den opdeling af venøs tromboemboli man ser i de fleste retningslinjer. Patienter med kræft samt patienter med uprovokeret venøs tromboemboli havde den højeste recidiv-risiko på cirka 20% efter 10 år. Mod forventning havde patienter med provokeret venøs tromboemboli også en høj risiko på mere end 15% efter 10 år. Derfor undlod vi den traditionelle arbitrære opdeling i ”provokeret” og ”uprovokeret” venøs tromboemboli, da vi i Studie 2 udviklede og internt validerede en køns-specifik risikoprædiktions-score til recidiv af venøs tromboemboli. Vi udviklede en velkalibreret risikoscore under akronymet AIM-SHA-RP. Endelig, med henblik på at forbedre compliance og behandling, undersøgte vi i Studie 3 potentielle faktorer, som vil kunne forudsige, hvilke patienter, der ikke opstarter blodfortyndende behandling efter første venøse tromboemboli. Op mod 24% opstartede ikke blodfortyndende behandling inden for 30 dage efter udskrivelse. De mest robuste prædiktorer for ikke at påbegynde behandling var demografiske eller relateret til

typen af den venøse tromboemboli, herunder kvinde køn, ung alder, samt dyb venetrombose.

Denne ph.d.-afhandling understreger det fortsatte behov for forbedret behandling og håndtering af patienter med venøs tromboemboli. Afhandlingen tydeliggør, at recidiv er hyppigt og at mange patienter modtager ingen eller ikke-optimal blodfortyndende behandling. Sammen med andre videnskabelige bidrag, kan studierne i denne afhandling bidrage til at optimere behandlingsmønstre med blodfortyndende medicin for de mange patienter med venøs tromboemboli.

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Ida Ehlers Albertsen, 2020.

LIST OF PAPERS IN THE THESIS

The thesis is based on the following three papers:

Paper 1.
Venous thromboembolism and risk of recurrence: a Danish nationwide cohort study. Albertsen IE, Nielsen PB, Søgaard M, Goldhaber SZ, Overvad TF, Rasmussen LH, Larsen TB. *Am J Med. 2018 ;131(9):1067-1074.e4.*

Paper 2.
Development of sex-stratified prediction models for recurrent venous thromboembolism: a Danish nationwide cohort study. Albertsen IE, Søgaard M Goldhaber SZ, Piazza G, Skjøth F, Overvad TF, Larsen TB, Nielsen PB. *Submitted to: Thrombosis and Haemostasis, December 2019.*

Paper 3.
Predictors of not initiating anticoagulation after incident venous thromboembolism a Danish nationwide cohort study. Albertsen IE, Goldhaber SZ, Piazza G, Overvad TF, Nielsen PB, Larsen TB, Søgaard M. *Am J Med. 2019. Doi: 10.1016/j.amjmed.2019.08.051.*

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BACKGROUND

INCIDENT VTE

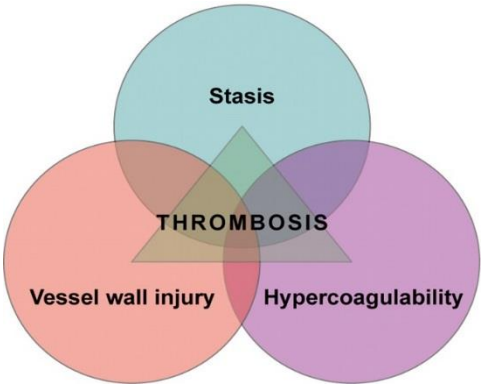
Venous thromboembolism (VTE) covers both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is when a thrombus is formed within the deep veins. DVT most often occurs in the legs, but can also form in the veins of the arms, and in the mesenteric and cerebral veins [1]. If a piece of the thrombus is dislodged from the deep veins, it can travel to the pulmonary arteries and form a, potentially fatal, PE.

VTE is the third leading vascular disease after myocardial infarction and stroke [2], and in 2010 almost 20.000 visits on to Danish hospitals concerned VTE [3]. The incidence rate of incident VTE is 1-2 per 1000 person-years and rises exponentially with increasing age [4]. In incident VTE patients, 30-40% debut with a PE [5].

VTE ranges from incidental, clinically unimportant VTE to massive embolism with sudden death. Patients suffering a VTE are at risk of developing chronic thromboembolic pulmonary hypertension [6], post thrombotic syndrome [7], recurrent VTE [5], and death [8,9]. A Danish population-based cohort study from 2014 showed that the mortality risks for patients with DVT and PE were markedly higher than for an age- and sex-matched comparison cohort without VTE during the first year, especially within the first 30 days (3.0% for DVT and 31% for PE versus 0.4% for controls) [8]. Considering both health-economic consequences as well as individual patient consequences, it is a disease of great importance to public health in general and the affected citizens [10].

VTE is a multifactorial disease, involving interaction between intrinsic factors of the patient (e.g. age, thrombophilia) and acquired exposures (i.e. surgery, hormone treatment, cancer) [11,12]. Of demographic factors, increasing age is an established risk factor, whereas no consensus exists about whether the incidence of VTE varies according to sex [1,11,13]. The so-called Virchow's Triad has delineated the basis for understanding the pathogenesis of VTE [14]. The theory proposes that VTE occurs as a result of: 1) stasis/alterations in the blood flow, 2) vessel wall injury and, 3) hypercoagulability (i.e., inherited or acquired hypercoagulable state) [Figure 1 – reproduced with permission from Kyrle et al. [15]]. Many patients with VTE fulfil one or more of Virchow's Triad and will therefore have a pro-thrombotic state.

Figure 1: Virchow's triad



The traditional concept of separation of risk factors and pathophysiology for VTE and atherosclerotic disease is being reconsidered [16]. VTE and atherothrombosis have shared risk factors and a common pathophysiology that includes inflammation, hypercoagulability, and endothelial injury [1]. Risk factors for VTE, such as cigarette smoking, hypertension, diabetes, and obesity, are often modifiable and overlap with risk factors for atherosclerosis [1,17]. Despite an overlap of the diseases, global public awareness is substantially lower for PE (54%) and DVT (44%) than heart attack (88%) and stroke (85%) [18].

The diagnosis of VTE is based on the clinical symptoms, D-dimer level, and relevant imaging examination [19]. Clinical signs and symptoms of PE and DVT are highly variable and unspecific but remain a cornerstone in the diagnostic strategy. Symptoms of DVT include pain, swelling, increased skin veins visibility, erythema, and cyanosis. In patients presenting with DVT symptoms, approximately 50% will have a co-existing PE [19]. However, only 5% of the DVT patients with co-existing PE will present with symptoms of a PE: including dyspnoea, hypoxia, sinus tachycardia, syncope, breast pain or haemoptysis [19]. Importantly, VTE patients might also present as asymptomatic or mimicking another disease, e.g. exacerbation of chronic obstructive pulmonary disease, consequently increasing a potential risk of physicians not recognizing the underlying VTE.

PROVOKED OR UNPROVOKED

Incident VTE is traditionally categorized as 'provoked' or 'unprovoked' depending on factors in the patient's medical history. In the literature, 'provoked' VTE is further sub-categorized according to whether the provoking factor was 'persistent' (i.e., active cancer), or whether the factor was a 'major transient' (e.g. surgery, immobilization), or 'minor transient' factor (e.g. oestrogen therapy, pregnancy, trauma/leg injury) [20]. 'Unprovoked' VTE is when no known provoking factor can be identified. Whether an episode of VTE was 'unprovoked' or 'provoked' has important prognostic and treatment implications. Most international guidelines base the recommendation of treatment duration on this simple dichotomization[21,22]. Patients with 'provoked' VTE are recommended shorter time-limited treatment whereas patients with 'unprovoked' VTE are recommended longer (> 3 months) "extended" treatment. Of note, patients with 'provoked' VTE due to active cancer are also recommended longer treatment duration.

While dichotomizing VTE as provoked or unprovoked, may seem appealing because of the apparent simplicity, the clinical picture is often much more nuanced. There is a large grey zone where precise categorization is not possible, and the term 'provoked' VTE is not clearly defined making consistent stratification challenging. It is well-established that major surgery is associated with VTE [23], and surgery is often referred to as 'a major (transient) risk factor' for VTE. But what about chronic inflammatory diseases? And does the recurrence risk then differ according to activity of the inflammatory disease? Are all kinds of trauma associated with an increased VTE risk? And what about driving a car for 6 hours with or without stopping for refuelling? In 2018 the International Society of Thrombosis and Haemostasis (ISTH) published a guideline on how to define a risk factor as a provoking (transient or persistent) [20]. According to the ISTH, a minor transient risk factors is: *"associated with a 3 to 10-fold increased risk of having a first VTE" or "associated with half the risk of recurrent VTE after stopping anticoagulant therapy (compared with if there was no transient risk factor), when the risk factor occurred up to 2 months before the VTE."* Although surely well intended, this definition can be difficult to translate into clinical practise practice.

RECURRENT VTE

Patients with incident VTE are known to carry a considerable risk of recurrence with an associated high mortality [8,24]. A meta-analysis from 2019 including 18 studies described a cumulative recurrence risk after 'unprovoked' VTE approaching 36% after 10 years [25]. However, VTE patients are heterogeneous and recurrence risk varies considerably according to patient characteristics [26–28]. Therefore, assessment of the VTE recurrence risk after acute VTE is a complex task.

Factors associated with recurrence include cancer, immobilization, and elevated body mass index [17,19]. Furthermore, male sex has been consistently associated with a higher risk of recurrence [17,29]. In a meta-analysis on 2554 patients with incident VTE investigating risk of recurrence, it was found that men had a 2.2-fold higher risk of recurrent VTE than women [29]. It is debated whether elevated D-dimer levels after discontinuing anticoagulation is associated with recurrence [30–32]. Furthermore, it is debated whether recurrence risk depend on the clinical manifestation of the incident event (if it is similar after proximal DVT and after PE) [12,33,34]. However, in patients with incident PE, VTE more frequently recurs as PE, while in patients who have had incident DVT, it tends to recur more frequently as DVT [12].

Anticoagulation is the keystone in VTE treatment and prevention of VTE morbidity, mortality, and recurrence. Anticoagulation is effective during treatment but do not eliminate the risk of subsequent recurrence after the discontinuation [35]. An increased risk of recurrence is found in the first 3- 6 months after anticoagulation cessation after which recurrence rates decline [25,33,36]. However, while a patients individual risk of recurrence may decline over time, the risk for major bleeding while treated remains constant [37].

Optimal duration of anticoagulation is a key issue in VTE management and largely dependent on the recurrence risk. However, estimates on recurrence risk after 10 years follow-up is sparsely investigated and vary widely, ranging from 25% to 40% [24,25,33,38,39] (see Table 1 for selected key studies on recurrence risk). Comparison between studies investigating VTE recurrence risk is challenging due to several epidemiologic issues: the definition of 'provoked' VTE varies throughout the literature; some studies are confined to patients with DVT others to patients with PE; the issue of death as a potential competing risk for recurrence has rarely been taken into account; and finally, some studies are restricted to patients with

'provoked' VTE, some to patients with 'unprovoked' VTE, and some include both types (Table 1).

The recurrence risk according to the VTE categorization used in guidelines is sparsely investigated [39]. However, based on available scientific evidence it is anticipated that patients with 'provoked' VTE represent a low-risk group with regards to recurrence of VTE. This is also reflected from the recommendation of time-limited duration of anticoagulant treatment in guidelines [21,22]. One study investigated recurrence risk according to all three VTE types: 'unprovoked', 'provoked', and 'cancer-related' VTE [39]. However, the study only included 166 patients with cancer – none of which were alive after 10 years. Therefore, they were not able to estimate long-term (10 year) recurrence risk for this group. The study reported 5-year cumulative incidence proportions: 28% for patients with 'unprovoked' VTE, 14% for patients with 'provoked' VTE, and 11% for patients with cancer. In conclusion, uncertainty remains in estimates of the long-term risk of recurrent VTE if anticoagulation is discontinued [22]. This uncertainty is reflected in weak (grade 2B) recommendations of the extended treatment to patients with 'unprovoked' VTE.

Table 1: Selected studies of VTE recurrence risk

Study, year	Follow-up time	Type and number of incident VTE patients	Recurrence risk
Kniffin et al[40], 1994.	-	Unprovoked and provoked combined: 7,174 PE and 8,923 DVT.	DVT patients: CIP* (recurrent PE): 3 months: 0.6%, 6 months: 1.0%, 12 months: 1.7%, 24 months 2.5%. PE patients: CIP (recurrent PE): 3 months: 4.8%, 6 months: 6.3%, 12 months: 8.0%, 24 months 10.1%.
Schulman et al[41], 1995.	24 months	Unprovoked and provoked combined: 897 VTE.	123 recurrences. 6 weeks treated group CIP 2-years: 18%; 6 months treated group CIP: 9.5%..
Beyth et al[42], 1995.	6-8 years	Unprovoked and provoked combined: 124 DVT.	18 recurrences. CIP: 1-year: 6%, 5 year CIP: 13%.
Prandoni et al[43], 1996.	2 years	Unprovoked and provoked combined: 355 DVT.	78 recurrences. CIP: 2 years 17.5%, 5 years: 24.6%, 8 years: 30.3%.
Van Beek et al[44], 1997.	6 months	Unprovoked and provoked combined: 193 PE.	14 recurrences (8%).
White et al[45], 1998.	6 months	36,924 (provoked?) DVT.	Patients hospitalized for 3, 4, 5, and 6 days, the 6-month CIP of recurrence was 5.4%, 5.1%, 5.4%, and 6.0%.
Heit et al[38], 2000.	Median 7.4 years	Unprovoked and provoked combined: 1,719 VTE.	404 recurrences. CIP: 7 days 1.6%, 30 days: 5.2%, 180 days: 10.1%, 1 year: 12.9%, 10 years CIP: 30.4%.
Hansson et al[46], 2000.	3-23 months	Unprovoked and provoked combined: 738 DVT.	109 recurrences (18.4%). CIP: 1 year: 7.0%, 2 years: 12.1%, 3 years: 15.0%, 4 years: 17.9%, 5 years: 21.5%.
Baglin et al[47] 2003.	24 months	Unprovoked and provoked combined: 570 VTE.	CIP: 2-year: 11%. Patients with unprecipitated VTE: CIP 2-year: 20% Patients with non-surgical triggers for a first VTE: CIP 2-year: 8%.
Prandoni et al[24] 2007.	Median 50 months	Unprovoked: 864 VTE. Provoked VTE: (Excl. cancer): 762 VTE.	Unprovoked 268 recurrences (31%) CIP: 1-year: 15.0% Provoked: 105 recurrence (14%) CIP 1-year: 6.6% Combined CIP: 1 year: 11.0%, 3 year: 19.6%, 5 year: 29.1%, 10 year: 39.9%.
Rodger et al[48], 2008. (HERDOO2)	18 months	Unprovoked: 646 VTE.	91 recurrences (14.09%) Annual risk 9.3%.
Eichinger et al[49], 2010. (Vienna)	43.4 months	Unprovoked: 929 VTE.	176 recurrences (18.9%). 1-year rate: 8.9%.
Tosetto et al[50], 2012. (DASH)	Median 22.4 months	Unprovoked: 1,818 VTE.	Only predicted risks of recurrence according to score level. Score=1: annual risk: 3.1%, score >1 annual risk: 9.3%.

Table 1 continued Study, year	Follow-up time	Type and number of incident VTE patients	Recurrence risk
Martinez et al [33], 2014.	Up to 10 years	Unprovoked: 16,708 VTE. Provoked: 12,073 VTE (Excl. cancer).	Unprovoked: Complete IR: 3.8/100PY** Provoked: Complete IR: 5.6/100PY Combined: 10-year CIP: 25.2%, 6-month IR: 11/100 PY, after that: 2/100 PY.
Huang et al[51], 2015.	3 years	Unprovoked and provoked combined: 2,334 VTE.	CIP: 30 days: 2.9%, 1 year: 7.2%, 3 year: 11%.
Moreno et al[52], 2016. (DAMOVES)	21.3 months	Unprovoked: 398 VTE.	65 recurrences (16.3%). Only relative risks reported.
Arshad et al[39], 2016.	Median 7.7 years	Unprovoked and provoked: 710 VTE	114 recurrences. Unprovoked CIP: 5 years: 17.9% Provoked CIP: 5 years: 16.7% Cancer CIP: 5 years: 26.4% Combined CIP: 10 year: 28%.
Rodger et al[53], 2016.	Mean 5 years	Unprovoked: 663 VTE.	165 recurrences. CIP: 8-year: 29.6%
Kahn et al [25], 2019.	Review	Unprovoked: 7,515 VTE.	CIP: 2-year: 16%, 5-year: 25%, 10-year: 36%.
Timp et al [54], 2019. (L-TRRiP)	Median 5.7 years	Unprovoked and provoked: 3,750 VTE.	507 recurrences. CIP (combined): 2 years: 7.4%, 4 years: 11.7%, 6 years: 15.0%, 8 years: 17.0%.

CIP: cumulative incidence proportion, **PY: patient-years.

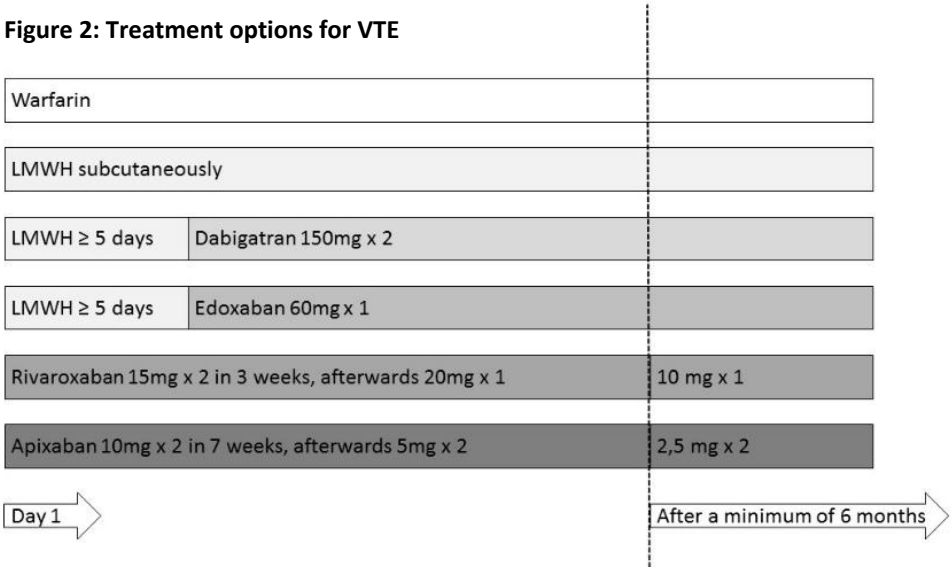
ANTICOAGULANT TREATMENT OF VTE

The aim of anticoagulation after an acute VTE is initially to prevent growth and embolization of the thrombus, and additionally to prevent sequelae, e.g., post thrombotic syndrome or chronic pulmonary hypertension [19]. This is initially an acute treatment that should be given to *all* patients presenting with VTE [12,55]. Minimum treatment duration is currently 3 months. The haemodynamically instable patient might also initially need reperfusion treatment, e.g. surgical embolectomy, percutaneous catheter-directed treatment, or thrombolytic therapy [12]. Uncertainty remains with regard to optimal treatment of patients with isolated distal DVT where recommendations in guidelines are vague [21,22]. However, in practice, most of these patients are also treated with anticoagulation [56].

For many years, vitamin K antagonists (VKA) were the only available class of oral anticoagulants, and therefore the standard of care for VTE treatment. In the last decade, non-vitamin K antagonist oral anticoagulants (NOACs) have been approved for treatment of VTE. In 2012, rivaroxaban was the first NOAC to be approved for VTE treatment in Denmark [57]. NOACs have not only intrinsic advantages such as rapid onset of action and wide therapeutic windows, but also a lower risk of intracranial, and fatal bleeding in VTE patients compared with VKA (i.e. warfarin) [58,59]. Furthermore, NOACs do not require laboratory monitoring and have fewer drug and food interactions than VKA.

The NOACs include the direct thrombin inhibitor dabigatran and direct Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. Treatment with dabigatran and edoxaban requires at least 5 days of bridging with low-molecular-weight heparin, whereas apixaban and rivaroxaban can be administered directly without heparin lead-in (see Figure 2). Until recently, low-molecular-weight heparin was the only recommended treatment option for patients with cancer-associated thrombosis, but guidelines now include edoxaban and rivaroxaban as treatment options for cancer patients with acute VTE, who have a low risk of bleeding and no potential drug-drug interactions with current systemic anticancer therapy [12,60–62].

Figure 2: Treatment options for VTE



The 2019 European Society of Cardiology (ESC) guidelines from European Heart Journal, recommend use of NOAC as first-choice treatment for VTE in patients eligible for a NOAC [12]. However, limited data exist on the safest and most effective NOAC due to lack of head-to-head trials comparing the NOACs [58,63]. The COVET Trial (Comparison of Oral Anticoagulants for Extended VEnous Thromboembolism; NCT03196349) was set-up to compare warfarin vs. rivaroxaban vs. apixaban for 12 months of extended treatment after 3-12 months initial treatment for 'unprovoked' VTE. However, according to clinicaltrials.gov recruitment status is "terminated (lack of enrolment)" and was "last updated August 2019" (site visited November 2019). Consequently, no NOAC is recommended over another. The choice of a specific NOAC is often based on physician and patient preferences, availability and reimbursement [58].

EXTENDED TREATMENT

After the acute treatment period (minimum 3 months), the aim of the extended treatment, is to prevent VTE recurrence over the long-term. Oral anticoagulants are highly effective in preventing recurrent VTE during treatment, but they do not eliminate the risk of subsequent recurrence after the discontinuation of treatment [35]. As shown in the PADSIS-PE (Prolonged Anticoagulation During Eighteen Months vs Placebo After Initial Six-month Treatment for a First Episode of Idiopathic

Pulmonary Embolism) trial, the clinical benefit is not maintained when anticoagulation is stopped [35]. In the PADIS-PE trial, 371 patients with 'unprovoked' PE were initially treated with warfarin for 6 months. After this period, patients were randomized to either additional 18 months warfarin treatment or to placebo. During the 18 months treatment period, the study found a hazard ratio (HR) of 0.22 (95% Confidence Interval (CI) 0.09; 0.55) for the risk of the composite endpoint of recurrent VTE and major bleeding in favor of additional therapy. This result was driven by a reduction in the risk of recurrent VTE: major bleeding occurred in 4 patients in the warfarin group and in 1 patient in the placebo group (HR 3.96; 95% CI 0.44; 35.89), and recurrent VTE occurred in 3 patients in the warfarin group and 25 patients in the placebo group (HR 0.15; 95% CI 0.05; 0.43). However, the benefit of anticoagulation in reducing recurrence was lost after anticoagulation was discontinued. In the 2 years posttreatment follow-up period, the recurrence risk in the warfarin group increased. At the end of follow-up, the risk in the warfarin group resembled the risk of the placebo group [35]. Same results were found when repeating the study with patients with DVT instead of PE [64]. Hence, time-limited treatment durations seem to merely delay but not entirely prevent recurrent events [35]. However, continuing anticoagulation is associated with a potential harm due to the risk of major bleeding, which can be fatal. Hence, optimal duration of the extended anticoagulation is both a crucial scientific and clinical concern.

The relative safety of NOACs over VKAs has led to considerations for extended, rather than limited, duration of anticoagulation therapies for VTE [59]. Both dabigatran, apixaban and rivaroxaban have all been investigated in randomized trials for extended treatment (after initial acute treatment in 3-18 months) (Table 2). Edoxaban has not yet been investigated for extended VTE treatment. The tested drugs have all been proven effective in reducing recurrence risk compared to placebo, but the benefit is partially offset by a risk of bleeding. Sulodexide and acetylsalicylic acid and have also been investigated for extended treatment, but are only recommended to patients who refuse to take or are unable to tolerate any form of oral anticoagulants [12]. Sulodexide is a mixture of low-molecular-weight heparin and dermatan sulphate, not standardly used in Denmark. The findings on extended therapy suggest a shift of the risk-benefit balance in favour of extended treatment.

Heterogeneity between the NOAC trials complicates indirect comparisons. The proportion of patients with 'provoked' VTE varies from approximately 60% in EINSTEIN-Choice [65] (Reduced-dosed Rivaroxaban in the Long-term Prevention of

Recurrent Symptomatic Venous Thromboembolism) to approximately 8% in AMPLIFY-Ext [66] (Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment) (the proportions in RE-MEDY and RE-SONATE are not reported). Duration of the acute treatment phase varies from 3-18 months and the duration of the extended period varies in a span of 6- to 36 months between the NOAC trials. Consequently, no certain answer can be given on which anticoagulant drug to choose to best balance the benefit of preventing recurrent VTE and minimize the harms of bleeding.

To guide treatment duration, American guidelines categorize patients with incident VTE as 'provoked' or 'unprovoked' [22]. Extended treatment is recommended to patients with low bleeding risk and 'unprovoked' proximal DVT or PE and to patients with active cancer and low bleeding risk (Table 3) [22]. Extended treatment is defined as 3 months to indefinite anticoagulant therapy where the continuing use of treatment should be reassessed at periodic intervals (e.g., annually), patient preference considered, and the choice of anticoagulant regimen re-evaluated [22].

In the 2019 ESC Guidelines [12] VTE patients are categorized according to the risk of recurrence over the long-term in: low risk (<3% per year) comprising patients with major transient or reversible risk factors; intermediate risk (3-8% per year) comprising patients with transient or reversible risk factors, non-malignant persistent risk factors, and no identifiable risk factors; and high risk (>8% per year) comprising patients with active cancer, previous VTE, and antiphospholipid antibody syndrome (Table 4) [Table reproduced with permission from Konstantinides et al. [12]]. All patients except those with an estimated "low risk" should therefore be considered for extended anticoagulation. These recommendations were raised from a recommendation 2b to a 2a in the latest guideline update. Linguistically, this means that extended treatment "should" be considered instead of "could". However, whether using the classification "provoking" risk factor or the terminology using "transient/persistent" risk factors, the dilemma remains on when exactly to define a factor as so.

Despite advantages of the NOAC's, underuse of anticoagulation and low medication adherence is still a matter of concern [9]. Non-initiation of anticoagulation is a global challenge that has been demonstrated both among patients with atrial fibrillation and VTE. A registry-based study from Denmark investigating anticoagulant therapy and mortality after VTE found that 21.3% of PE patients and 34.9% of DVT patients did not fill a prescription for anticoagulation

within 30 days [9]. However, the study did not investigate predictors associated with non-initiation to possibly decrease the high proportion of untreated VTE patients.

Table 2: Clinical trials on extended treatment of VTE (moderated version adapted from ESC guidelines [23]).

Active*	Study, year	Comparison	No. patients enrolled	Patients with index PE	Treatment duration	VTE rate in control group	Risk reduction for recurrence (HR; 95% CI)	Major or CRNM bleeding in intervention* group (HR; 95% CI)
Dabigatran	RE-SONATE, 2013 [67]	Placebo vs. dabigatran 150 mg b.i.d.	1343	33%	6-18 months	5.6%	92% (0.08; 0.02-0.25)	5.3% (2.92; 1.52- 5.60)
	RE-MEDY, 2013 [67]	Warfarin (INR 2-3) vs. dabigatran 150 mg b.i.d.	2856	35%	18-36 months	1.3%	Risk difference, 0.38% vs. VKA (1.44; 0.78-2.64)	5.6% (0.54; 0.41- 0.71)
Rivaroxaban	EINSTEIN Extension, 2010 [68]	Placebo vs. rivaroxaban 20 mg o.d.	1196	38%	6-12 months	7.1%	82% (0.18; 0.09-0.39)	6.0% (5.19; 2.3 -11.7)
	EINSTEIN Choice, 2017 [65]	Aspirin 100 mg o.d. vs. rivaroxaban 20 mg o.d. rivaroxaban 10 mg o.d.	3365	49%	12 months	4.4%	66% (0.34; 0.20-0.59; R 20 mg vs. aspirin) 74% (0.26; 0.14-0.47; R 10 mg vs. aspirin)	3.3% (1.59; 0.94- 2.69) 2.4% (1.16; 0.67- 2.03)
Apixaban†	AMPLIFY Extension, 2013 [66]	Placebo vs. apixaban 5 mg b.i.d. vs. apixaban 2.5 mg b.i.d.†	2486	35%	12 months	8.8%	80% (0.36; 0.25-0.53; apixaban 5 mg vs. placebo) 81% (0.33; 0.22-0.48; apixaban 2.5 mg vs. placebo)	4.3% (1.62; 0.96- 2.73) 3.2% (1.20; 0.69- 2.10)
Aspirin	WARFSA, 2012 [69]	Placebo vs. acetylsalicylic acid 100 mg o.d.	402	40%	≥24 months	11.2%‡	40% (0.58; 0.36-0.93)	1.0% (0.98; 0.24-3.96)
	ASPIRE, 2012 [70]	Placebo vs. acetylsalicylic acid 100 mg o.d.	822	30%	2-4 years	6.5%‡	26% (0.74; 0.52-1.05)	1.1%
Sulodexide	SURVET, 2015 [71]	Placebo vs. sulodexide 500 lipasemic units b.i.d.	617	8%	24 months	9.7%	51% (0.49; 0.27-0.92)	0.6% (0.97; 0.14-6.88)

b.i.d. = twice a day; CI = confidence interval; CRNM = clinically relevant non-major; HR = hazard ratio; INR = international normalized ratio; o.d. = once a day; PE = pulmonary embolism; R = rivaroxaban; VKA = vitamin K antagonists; VTE = venous thromboembolism.

* 'Intervention' denotes the anticoagulant tested in the table; the comparator arm also received anticoagulation (a VKA) in some of the studies. (Edoxaban has not been investigated for extended treatment).

†The approved dose of apixaban for extended treatment.

‡Incidence per patient-year.

Table 3: Duration of anticoagulation in patients with VTE* according to American CHEST guidelines [22].

Place of VTE	Type of VTE	Duration of treatment (recommendation¶)
Isolated distal DVT †	Provoked	3 months§ (Grade 1B)
	Unprovoked	3 months§, then evaluation for of the risk-benefit ratio of for extended therapy • Low/moderate bleeding risk: 3 months (Grade 2B) • High bleeding risk: 3 months (Grade 1B)
Proximal DVT or PE ‡	Provoked	3 months (Grade 1B/Grade 2B)
	Unprovoked	At least 3 months, then evaluation of risk-benefit ratio of for extended therapy • Low/moderate bleeding risk: extended therapy‖ (Grade 2B) • High bleeding risk: 3 months (Grade 1B)
Second unprovoked VTE		• Low bleeding risk: extended therapy‖ (Grade 1B) • High bleeding risk: 3 months (Grade 2B)
VTE and active cancer		• Low/moderate bleeding risk: extended therapy‖ (Grade 1B) • High bleeding risk: extended therapy‖ (Grade 2B)

*VTE: venous thromboembolism, †DVT: deep venous thromboembolism, ‡ PE: pulmonary embolism, §If decision has been made to treat with anticoagulant therapy, ‖In all patients who receive extended (3 months to indefinite) anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g., annually), patient preference considered, and the choice of anticoagulant regimen re-evaluated. ¶Recommendation: strong (Grade 1) and weak (Grade 2) recommendations based on high-quality (Grade A), moderate-quality (Grade B), and low-quality (Grade C) evidence.

Table 4: Categorization of risk factors for VTE based on risk of recurrence over the long-term* according to ESC guidelines [12].

Estimated risk for long-term recurrence*	Risk factor category for index PE	Examples†
Low (< 3% per year)	Major transient or reversible factors associated with > 10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anesthesia for >30 min • Confined bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤ 10-fold increased risk for first (index) VTE	• Minor surgery (general anesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Estrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (> 8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

*If anticoagulation is discontinued after the first 3 months. †The categorization of risk factors for the index VTE event is in line with that proposed by the International Society on Thrombosis and Haemostasis [20].

RISK OF BLEEDING

A meta-analysis on 6 phase 3 trials compared the efficacy and safety of NOAC's versus VKA in the acute treatment of VTE [59]. Recurrent VTE occurred in 2.0% of NOAC recipients compared with 2.2% in VKA recipients (relative risk (RR) 0.90, 95% CI 0.77; 1.06) [59]. Furthermore, treatment with a NOAC significantly reduced the risk of major bleeding (RR 0.61, 95%CI 0.45; 0.83) [59]. In the VTE extension studies on NOACs, major bleeding or clinically relevant non-major bleeding occurred in 2-6% of the patients in the intervention groups (dabigatran[67], rivaroxaban[65,68], and apixaban [66]) (Table 2). In a study from 2014 using data from a prospective, non-interventional, oral anticoagulation registry of 1,776 daily care patients (Dresden NOAC registry) treated with rivaroxaban, major bleeding occurred in 6.1% with an annual major bleeding rate of 4.1 (95% CI 2.5-6.4) per 100 patient-years (py) [72]. The patients were treated with rivaroxaban for a median of 274 days. However, despite different treatment regimens, uncertainty remains in estimates of the long-term risk of major bleeding if treatment is continued. Also, since patients at high bleeding risk were excluded from the NOAC extension studies, the safety of the drugs in these patients still needs clarification.

Several bleeding risk scores have been developed to help evaluate the risk of bleeding. Some of the most frequently used bleeding scores include the HAS-BLED score [73], originally developed to assess bleeding risk in patients with atrial fibrillation using VKAs, the VTE-BLEED score [74], and the ACCP scheme [22]. The two latter VTE-specific bleeding scores are developed for patients with 'unprovoked' VTE only.

Individual studies have validated the predictive performance of the bleeding risk scores [75–77]. However, a review from 2017 concluded that none of the bleeding scores could be used to guide decisions about extended treatment for secondary prevention of recurrent event in patients with 'unprovoked' VTE [78]. Of note, the review did not include the HAS-BLED score. The review concluded that the discriminatory performance was too poor and that the scores had been insufficiently evaluated in appropriate patient populations. They recommended that clinicians use clinical knowledge to assess the risk-benefit ratio on well-established risk factors in this patient population [78]. On the contrary, a study from 2019 evaluated the ability of the VTE-BLEED score using a Japanese multicentre registry (the COMMAND VTE Registry) [79]. They concluded that the VTE-BLEED score could be useful for assessment of bleeding risk and hence the optimal duration of

anticoagulation therapy in individual patients [79]. In 2019 ESC guidelines, it is suggested to reassess bleeding risk periodically (e.g., once a year in patients at low risk, and every 3 or 6 months in patients at high risk for bleeding) either by implicit judgement after evaluating individual risk factors or by the use of a bleeding risk score at the time of initiation of anticoagulant treatment [12]. They do not recommend use of one score over another. The American guidelines list their own (ACCP) scheme to determine bleeding risk [22].

The newly developed reversal agents for the NOACs may support the paradigm shift towards extended treatment duration. Additionally, there is an ongoing search for anticoagulants that will exert anti-thrombotic effects without impeding haemostasis and thus theoretically without causing major bleeding complications. Coagulation factors XI and XII have been identified as promising targets [80]. While these new targets for anticoagulation are continuously being investigated, the search for the optimal duration of anticoagulation for the individual patient continues [80].

RISK STRATIFICATION FOR VTE RECURRENCE

Treatment of VTE patients should add up to a net clinical benefit in favour of a reduced recurrence risk without an excess risk of bleeding. Risk stratification and prediction models may aid clinicians in such decision-making situations. Risk prediction models have also become increasingly popular in the era of “shared decision-making” aiming at including both the patient’s and physician’s perspective when deciding on realistic treatment plans. However, despite many models published in the academic literature, most models are never translated into useful tools for the clinician [81]. When developing risk scores, we therefore have to consider: “are we just adding to the heap or closing a gap?” [82].

VTE prediction models have been developed [48–50,52,54] (see Table 5). However, none of the existing VTE recurrence risk models are recommended in guidelines and they have only been sparsely validated [54,83–86]. Therefore, to navigate the dilemma and guide anticoagulant treatment duration, most guidelines recommend the basic stratification with classification of the incident VTE event as ‘provoked’, ‘cancer-related’ or ‘unprovoked’ depending on risk factors in patients’ medical history [21,22]. A clinically useful stratification would identify patients with high risk of recurrence requiring continued treatment and, conversely, patients with a shorter, time-

limited need for treatment. This would enable treating physicians to make the best possible choices regarding duration of anticoagulation. However, if this is not the case, it will add to the current dilemmas in VTE treatment management.

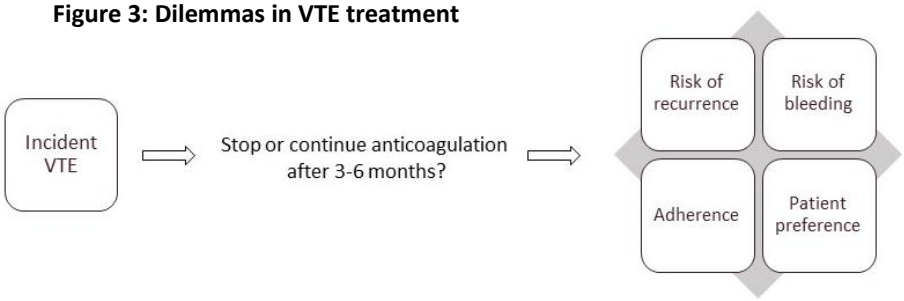
Table 5: Prediction models for risk of recurrent VTE

	HER DOO2 (2008) [48]	Vienna (2010) [49]	DASH (2012) [50]	DAMOVES (2016) [52]	L-TRRiP (2019) [54] (Model C)
Patients (Recurrences)	646 (91)	929 (176)	1818 (239)	398 (65)	3750 (507)
Design	Prospective cohort	Prospective cohort	Retrospective meta-analysis on 7 studies	Prospective cohort	Prospective cohort
Predictive Variables	For women: • HER: Hyper-pigmentation, Edema or Redness of either leg • D-dimer ≥ 250 µg/L while on warfarin • Obesity: BMI ≥ 30 • Old: Age ≥ 65	• Male sex • Location of first VTE • D-dimer after anti-coagulation	• D: Abnormal D-dimer after stopping anti-coagulation • A: Age < 50 • S: male Sex • H: VTE not associated with Hormonal therapy (in women)	• D-dimer: during treatment • Age (HR 1.03/decade) • Mutation: factor V Leiden and/or Prothrombin mutation • Obesity • Varicose veins • Eight: high factor VIII activity • Sex: male sex	• Male sex • Type and location of VTE • Surgery • Pregnancy/ • puerperium • Hormone use • Plaster cast • Immobility • Cardiovascular disease • Blood group • Factor V Leiden

UNANSWERED DILEMMAS IN VTE TREATMENT

As summarized, patients suffering a VTE carry a considerable risk of recurrent events. Therefore, incident VTE is initially an acute disease requiring anticoagulant treatment despite any other patient comorbidity. Nonetheless, a dilemma arises after the initial treatment period of 3 to 6 months: Should we stop or continue the anticoagulant treatment? Several aspects influence this decision [Figure 3].

Figure 3: Dilemmas in VTE treatment



Risk of recurrence and bleeding

The optimal duration of anticoagulation is one of the most vexing issues in VTE management and is largely dependent on the VTE recurrence risk. Furthermore, the recurrence risk must always be balanced against the risk of bleeding when receiving anticoagulation. However, as debated, VTE patients are a heterogeneous population with varying recurrence risk. Uncertainty remains of both the long-term risk of major bleeding if treatment is continued, and, importantly, the long-term risk of recurrent VTE if anticoagulation is discontinued [22].

Ideally, risk stratification should differentiate patients in groups above and or below well-defined risk thresholds that allow guidance of clinical decision-making in relation to treatment duration. As reviewed above, most guidelines recommend a simplistic dichotomization in 'provoked'/'unprovoked' while no clear definition for the term 'provoked VTE' exists. No other risk stratification tool is recommended in guidelines and recommendations remain imprecise with respect to treatment duration [12,21,22].

Adherence and patient preference

Adherence to medication is a prerequisite for successful treatment. During the shared decision making on anticoagulant treatment duration, patient preference is an important aspect to consider to ensure optimal adherence. Despite advantages of the NOAC's, underuse of anticoagulation and low medication adherence is still a matter of concern [9]. However, no previous studies have investigated predictors of non-initiation.

Research goals

This thesis is based on three studies ultimately aiming at more informed navigation in some of the dilemmas of VTE treatment. The studies focus on various perspectives regarding VTE recurrence, from clarifying contemporary VTE recurrence risk, developing a new risk stratification tool for recurrent VTE, to finally identifying potential predictors of not initiating anticoagulation after incident VTE. The thesis will provide a general discussion of issues surrounding recurrent VTE and present and debate the results of the three studies within this discussion. When referring to one of the papers in the thesis it is highlighted in bold: **Study 1/2/3**.

AIMS

The specific aims of the studies were:

Study 1
The aim of the first study was to describe the risk of recurrent VTE according to 'unprovoked', 'provoked' and 'cancer-related' incident VTE, representing the stratification used in most VTE guidelines.

Study 2
The aim of the second study was to develop and internally validate risk prediction scores for VTE recurrence for men and women separately, which may aid the decision of anticoagulant treatment duration for patients with incident VTE.

Study 3
To potentially improve treatment adherence, the aim of the third study was to investigate factors associated with not initiating anticoagulation after incident VTE.

SETTING AND STUDY POPULATION

Denmark has several advantages when it comes to registration of health data making it ideal for epidemiological large-scale cohort studies: 1) citizens with residency in Denmark are offered a free-of-charge tax-supported educational- and health-care system, where all medications are partly reimbursed; 2) all residents in Denmark hold a 10-digit unique identification number [87] enabling individual-level cross-linkage of data from numerous nationwide registries; and finally 3) government-maintained and funded nationwide registries, providing longitudinal sources of routinely collected administrative, health, and clinical quality data [88].

All three studies of this thesis were based on data from the Danish nationwide registries to identify patients with a VTE diagnosis. Via these registries, we had information on dates of admission and discharge diagnoses for more than 99% of all hospital admissions, sex, date of birth, vital status, and emigration status on all citizens; information on purchase date, Anatomical Therapeutic Chemical (ATC) classification codes, and package size for all prescriptions claimed; and information on socio-economic factors. The registries are described in more detail on page 69. Methods used to increase the positive predictive value (PPV) of both incident and recurrent VTE diagnoses are described under “Methodological Considerations” on page 71.

STUDY 1

Study 1 was made in cooperation with: Peter B. Nielsen, Mette Søgaard, Samuel Z. Goldhaber, Thure F. Overvad, Lars H. Rasmussen, and Torben B. Larsen [5].

Aim: In **Study 1**, we sought to investigate the risk of recurrent VTE according to the incident VTE categories suggested in guidelines: 'provoked', 'unprovoked' and 'cancer-related'.

Methods: Since no clear definition of 'provoked VTE' is available, we used available literature and guidelines to define 'provoked", 'unprovoked' and 'cancer-related' VTE. We linked data from nationwide Danish health registries (described on page 69) to identify all patients with incident VTE from January 2000 through December 2015. Incidence rates were calculated as number of events divided by 100 py and the absolute risk of recurrence, with no adjustment for anticoagulant treatment, was depicted as cumulative incidence functions by means of the Aalen-Johansen estimator, assuming death as competing risk.

Results: The study population comprised 73,993 patients with incident VTE (54.1% female and mean age 62.3 years). In the study population, 49% were categorized as having 'unprovoked' VTE, 38% with 'provoked', and 14% with 'cancer-related' VTE. At 6-month follow-up, the recurrence rates for patients with 'provoked' (6.92 per 100 py) and 'unprovoked' VTE (6.80 per 100 py) were similar (Table 6). Patients with cancer-related VTE had a higher recurrence rate (9.06 per 100 py). Recurrence rates at 10 years follow-up were 2.84 per 100 py for patients with 'unprovoked' VTE, 2.22 for patients with 'provoked' VTE, and 3.70 for cancer-related VTE.
At 6-month follow-up, the absolute recurrence risk for patients with 'provoked' and 'unprovoked' was similar (Figure 4A). Highest recurrence risk was found for patients with cancer. The cumulative incidence curve for patients with 'provoked' VTE diverged just after the 6-month mark, with an estimated absolute recurrence risk at 10-year follow-up of 15%. At the 10-year follow-up, the risks of 'unprovoked' and 'cancer-related' VTE were similar, with an absolute recurrence risk of approximately 20% for both types of VTE (Figure 4B) [5].

Conclusion: This study found that patients with 'cancer-related' VTE possessed the highest recurrence risk. At 6-month follow-up, risk of recurrence for patients with 'unprovoked' and 'provoked' VTE was similar. At 10-year follow-up, the risk of recurrence was comparable for patients with 'unprovoked' VTE and patients with

'cancer-related' VTE. A high recurrence risk in all types of VTE – including 'provoked' VTE – underscores that further research is needed to optimize risk stratification for VTE patients [5].

Figure 4: Cumulative risk of recurrent VTE by incident VTE type at 6-month (A) and 10-year (B) follow-up [5].

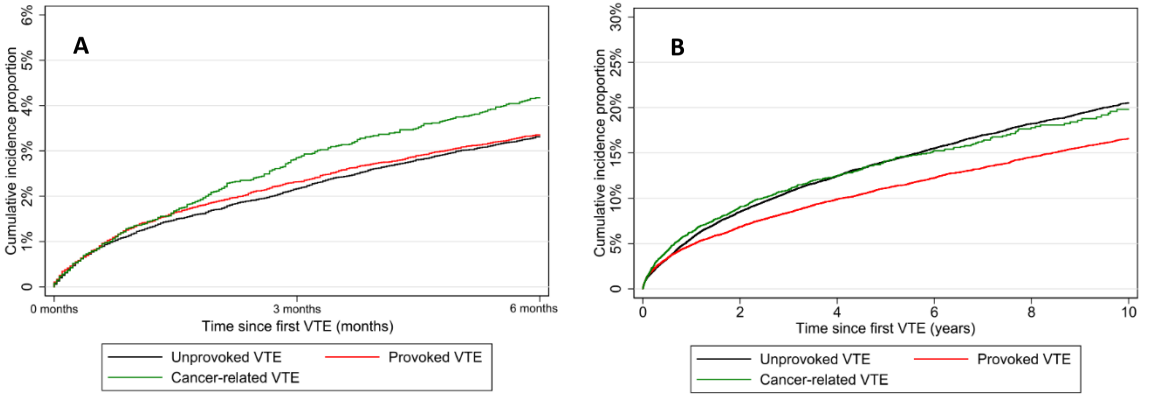


Table 6: Number of events and recurrence rates per 100 person-years according to incident VTE type [5].

Type of VTE	6-Month follow-up		10-year follow-up	
	Number of events	Recurrence rates/100py	Number of events	Recurrence rates/100py
Provoked VTE	913	6.92	3086	2.22
Unprovoked VTE	1167	6.80	4963	2.84
Cancer-related VTE	339	9.06	734	3.70

DISCUSSION AND PERSPECTIVES (STUDY 1)

Other studies reporting incidence rates show the same tendencies as found in **Study 1** with highest recurrence rates in the first months after incident VTE [25,33,39,89]. In line with our findings, a meta-analysis from 2019 on 18 studies investigating recurrence risk after 'unprovoked' VTE in patients discontinuing anticoagulation, described a 10-year recurrence rate similar to what we found of 3.1 per 100 patient years [25]. Their estimated cumulative risk of recurrence of 36% (95% CI 28%; 45%) after 10 years was somewhat higher than what we observed. Importantly, the review did not consider death as a competing event leading to possible overestimation of risk estimates [90]. Furthermore, only 3 of the 18 studies included in the meta-analysis provided 10 years of follow-up, and half of the studies were based on data more than a decade old.

As previously described, patients with 'provoked' VTE are traditionally considered at low risk for recurrence. However, in **Study 1**, we observed a similar recurrence risk among patients with 'provoked' and 'unprovoked' VTE during the first 6 months of follow-up. After this, the risk curves diverged to some extent. At 10-year follow-up, the recurrence risk for patients with 'provoked' VTE resembled the risk for patients with 'unprovoked' and cancer-related VTE. The patients with 'provoked' VTE are expected to be the low-risk group and yet, more than 15% had recurrence after 10-year follow-up.

The EINSTEIN-CHOICE trial [65] randomized patients with incident 'provoked' (60%) or 'unprovoked' (40%) DVT and/or PE who had completed 6-12 months anticoagulant treatment to either rivaroxaban (20 mg once daily or 10 mg once daily) or low-dose aspirin (100mg once daily). The study was in line with our observations by showing that the suspected 'low-risk' group had a high recurrence risk (see Table 7). In the group treated with 20mg rivaroxaban, 1.4% of the patients with 'provoked' VTE had recurrence one year after randomization, compared with 1.8% of the patients with 'unprovoked' VTE. In the aspirin arm, 3.6% of the patients with 'provoked' VTE had recurrent VTE versus 5.6% of the patients with 'unprovoked' VTE.

Table 7: Proportions of recurrent VTE one year after randomization in the EINSTEIN-CHOICE trial [65]

	Rivaroxaban, 20mg (N=1107)	Rivaroxaban, 10mg (N=1127)	Aspirin, 100mg (N=1131)
Provoked VTE (60%)	1.4%	0.9%	3.6%
Unprovoked VTE (40%)	1.8%	1.5%	5.6%

EINSTEIN-Extension (Once-daily Oral Rivaroxaban versus Placebo in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism) was a randomised trial comparing rivaroxaban with placebo for 6 or 12 months in DVT patients who had completed 6 to 12 months of treatment for VTE [68]. Prins et al. conducted a study [91] based on data from the EINSTEIN-CHOICE study [65] and the EINSTEIN-Extension study [68] to assess the risk of recurrence according to baseline profiles defined according to 'provoked' VTE further sub-divided in major/minor 'transient' or 'persistent' risk factors. They found that the risk of recurrent VTE in patients with trauma or major surgery (being 'major transient' risk factors) was 0% in both the rivaroxaban and aspirin groups. However, risk of recurrence in patients with VTE provoked by 'minor persistent' (e.g. congestive heart failure, inflammatory bowel disease) or 'minor transient' risk factors (i.e. immobilization, use of oestrogen therapy, pregnancy) were similar to the recurrence risk described in patients with 'unprovoked' VTE (1.8% and 0.4% versus 1.5% among patients treated with rivaroxaban).

Our conclusion from **Study 1**, with the findings of high recurrence risk both among patients with 'provoked' and 'unprovoked' VTE, were in line with the findings of the EINSTEIN-CHOICE and Prins et al. studies, underscoring that more research is needed to optimize risk stratification for VTE patients.

LACK OF DIFFERENTIATION

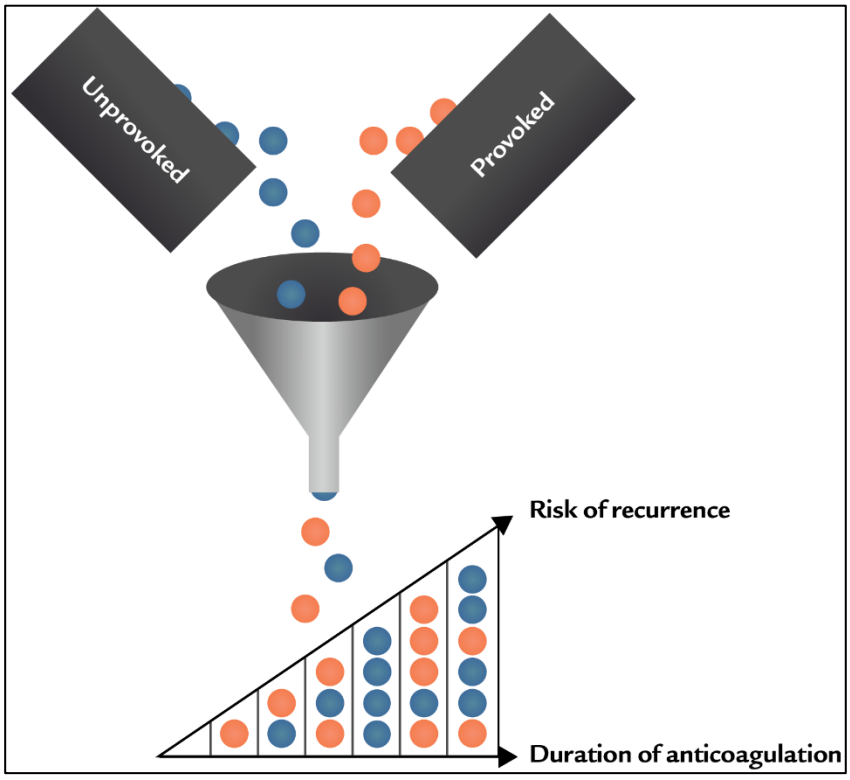
Another aspect to the dilemma of VTE recurrence and risk stratification arises, when it appears that 'provoked' VTE is also associated with high recurrence risk [5,65]. This group is traditionally considered low-risk and only recommended time-limited anticoagulation for 3 months. Nevertheless, our finding of recurrence risk higher than 15% at 10 years among patients with provoked VTE in **Study 1** argues against

this common belief. Conversely, guidelines recommend extended treatment for patients with 'unprovoked' and cancer-related VTE, who had a 10-year recurrence risk of approximately 20 % in **Study 1**. Ideally, risk stratification should differentiate patients in groups above and or below well-defined risk thresholds that allow guidance of our clinical decision-making in relation to treatment duration. The appreciable recurrence risk in the group of patients with 'provoked' VTE revealed in **Study 1**, certainly indicate that optimal VTE management could benefit from a more nuanced approach. Either we are bound to consider anticoagulants to patients with provoked VTE for a longer period of time, or otherwise we have to redefine our approach to risk stratification in order to identify those patients with a net clinical benefit justifying short-term treatment.

A REVISED STRATEGY FOR VTE RISK PREDICTION

The finding of a high recurrence risk seen across all VTE types combined with the continued challenge of how to define 'provoked' VTE, inspired the *On my Mind* piece published in Circulation in 2018: "Let's stop dichotomizing venous thromboembolism as provoked or unprovoked"[92], see Figure 5. That article was done in cooperation with Gregory Piazza and Samuel Z. Goldhaber.

Figure 5: Revised strategy for determining the optimal duration of anticoagulation after VTE [92].



The underlying idea is that determination of optimal duration of anticoagulation should be based on assessment of a patient's individual risk factors instead of a simplistic dichotomization. Refinement of the categories may improve identification of those patients with high recurrence risk who needs extended duration anticoagulation. Correspondingly, advanced risk stratification could also lead to improved identification of patients with a low recurrence risk, who can safely discontinue their treatment without fearing recurrence.

This idea was later on supported by the 2019 ESC guideline on the diagnosis and management of acute pulmonary embolism that "no longer support the terminology 'provoked' and 'unprovoked', as it is "potentially misleading and not helpful for decision-making regarding the duration of anticoagulation" [12].

Altogether, this laid the foundation for the idea of a new prediction model to estimate recurrence risk after both ‘provoked’ and ‘unprovoked’ incident VTE.

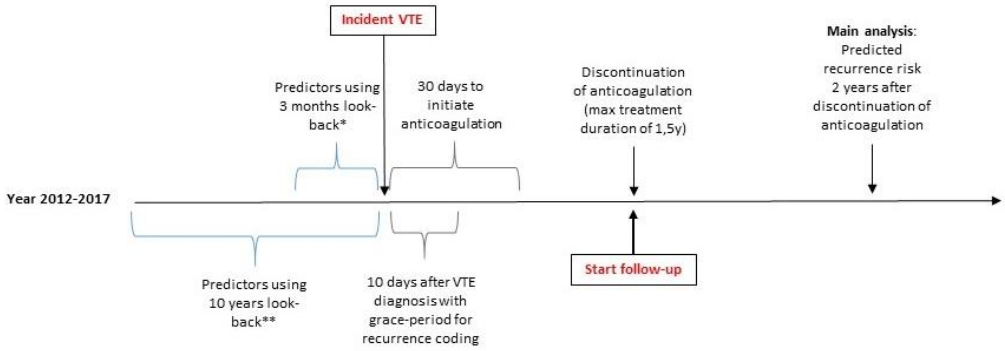
STUDY 2

Study 2 was made in cooperation with: Mette Søgaard, Samuel Z. Goldhaber, Gregory Piazza, Flemming Skjøth, Thure F. Overvad, Torben B. Larsen, and Peter B. Nielsen [93].

Aim [93]: **Study 2** aimed to develop and internally validate two clinically applicable sex-specific prediction models for assessing VTE recurrence risk among patients with incident VTE, disregarding the traditional division in 'provoked' and 'unprovoked' VTE.

Methods [93]: Using the Danish registries, we identified all cancer-free routine care inpatients and outpatients with completed oral anticoagulant treatment for incident VTE from January 2012 through December 2017. The outcome was recurrent VTE within 2 years (the study design is depicted in Figure 6). Start of follow-up was at the time of discontinuation of oral anticoagulation, with a maximum treatment period of 1.5 years. Two sex-specific risk scores were derived using a Cox regression analysis and a backward selection process on a set of 24 potential predictors. Performance of the models was assessed through calibration and discrimination using bootstrap techniques to internally validate the scores.

Figure 6: Timeline of Study 2 [93].



Results [93]: The study included 11,519 incident VTE patients with completed OAC treatment, 53.4% were men and the mean age was 62.6 years. Among men, 589 (10%) suffered recurrent VTE during two years of follow-up; for women, the

number was 377 (7%). We developed risk scores under the joint acronym AIM-SHA-RP (Table 8). Predictors for both sexes were: Age, Incident pulmonary embolism, and recent Major surgery; predictors specifically for men were: Statin treatment, Heart disease and Antiplatelet treatment, while chronic Renal disease and recent Pneumonia or sepsis were predictors specifically for women. Both risk scores were well calibrated (Figure 7) and they identified a low-risk group with recurrence risk of <5% (3% men, 7% women), a group with intermediate recurrence risk between 5-10% (7% men, 73% women), and a group with high recurrence risk of >10% (90% men, 20% women) for both sexes. Generally, discriminative capacities, as measured by the c-statistic, were modest.

Conclusion [93]: We developed two new risk prediction scores under the joint acronym AIM-SHA-RP for men and women. The models were designed to disregard the traditional division in 'unprovoked' and 'provoked' incident VTE. Age, Incident PE, recent Major surgery, Statin treatment, Heart disease, Antiplatelet treatment, chronic Renal disease and recent Pneumonia/sepsis were all included in the scores. These new risk scores may prove useful as tools for shared decision making to guide the duration of anticoagulation after incident VTE in everyday clinical practice [93].

Table 8: Final scores for 11,519 men and women [93].

AIM-SHA-RP: Age Incident PE Major surgery – Statin Heart disease Antiplatelet – Renal disease Pneumonia/sepsis			
Men ♂		**Women ♀**	
Variable	**Points**	**Variable**	**Points**
Age > 50 years	+1	**A**ge > 60 years	+2
Incident pulmonary embolism	+1	**I**ncident pulmonary embolism	+1
Recent **M**ajor surgery*	-2	Recent **M**ajor surgery*	-2
Statin treatment‖	-1	Chronic **R**enal disease‡	-1
Previous **H**eart disease§	+1	Recent **P**neumonia or sepsis†	-1
Antiplatelet treatment‖	-1		
Score sum		**Score sum**	
Low risk: <5%	< -1		< 0
Intermediate risk: 5-10%	-1		0-2
High risk: >10%	> -1		> 2

*Within 3 months operation with following operation-codes: KA, KB, KD, KF, KG, KH, KJ, KK, KL, KM, KN, KP, KMCA

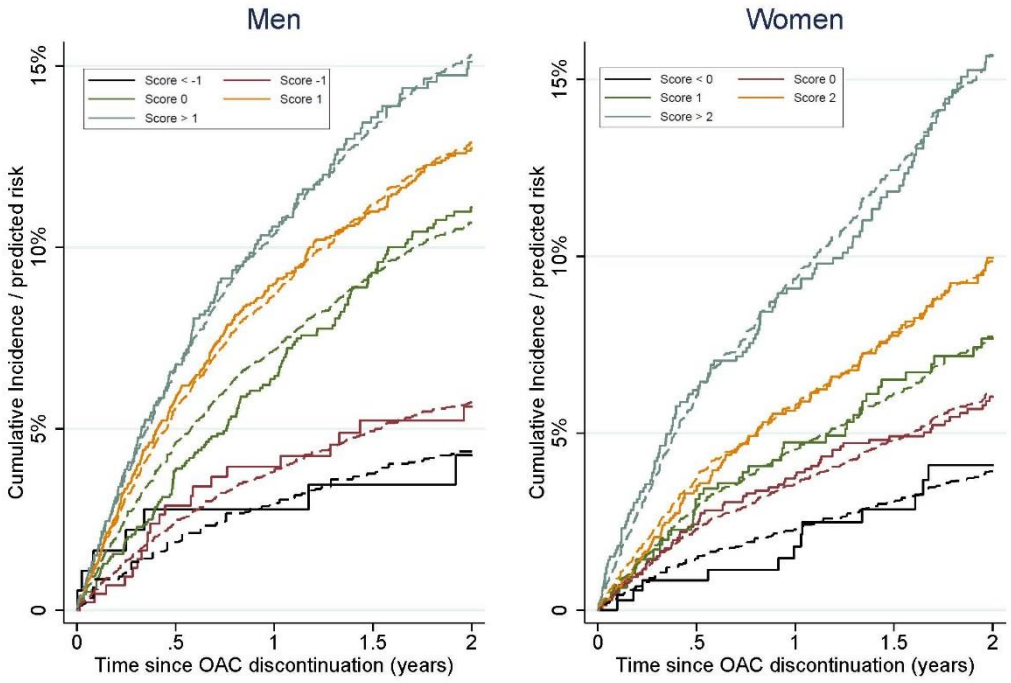
§Within 10 years: stroke, cardiac arrest, ischemic heart disease or congestive heart failure, ICD-10 codes: I60, I61, I62, I63, I64, I46, I20 I21 I22 I23 I24 I25, I50, I110, I130, I132, I420

‖Treatment within one year before incident VTE, ATC-codes: antiplatelet: B01AC04, B01AC06, statins: C10

†Within 3 months hospitalized with sepsis or pneumonia, ICD-10: A40, A41, J12, J13, J14, J15, J16, J17, J18

‡Within 10 years: chronic kidney disease, unspecified kidney failure, chronic nephritic syndrome, or chronic tubulointerstitial nephritis, ICD-10: N00, N01, N03, N05, I12, I13, I15.0, I15.1, N11, N14, N15, N16, Q61.1-61.4, N18, N19, N26, N27, N07, N08.

Figure 7: Observed and predicted risk of recurrent VTE for men and women according to AIM-SHA-RP score levels [93].



Solid lines: observed cumulative recurrence risk; dashed lines: predicted recurrence risk

DISCUSSION AND PERSPECTIVES (STUDY 2)

The two new prediction models developed in **Study 2** are intended to be used as a tool for shared decision-making based on predictions of future risk for recurrent VTE both for patients presenting with 'unprovoked' and 'provoked' VTE. This is in contrast to most previous prediction models for VTE recurrence developed only for patients with 'unprovoked' VTE [48–50,52]. Study 2 identified, for both sexes, a low-risk group defined as an estimated 2-year recurrence risk of < 5%, an intermediate risk group with an estimated 2-year recurrence risk between 5-10%, and a group with high recurrence risk, defined as >10% 2-year recurrence risk.

Low recurrence risk

Treatment of VTE with a NOAC compared with warfarin has been found to reduce the risk of major bleeding [59]. However, limited data exist regarding safety of the agents in extended periods beyond 6 to 36 months [63]. As NOACs may be proven increasingly safe for extended treatment, the tipping-point of who to offer extended treatment may be shifted towards an even lower threshold, e.g. > 3% recurrence risk after 2 years. Until a new threshold is defined, the AIM-SHA-RP scores may support the decision to discontinue treatment for patients in the low-risk groups. Patients with an estimated low risk of < 5% recurrence risk should not continue anticoagulation treatment according to contemporary guidelines [94]. In Study 2, the low risk group comprised 3% men and 7% women.

Intermediate recurrence risk

The groups identified with intermediate risk (7% men, 73% women) should be advised to continue treatment, but also continue yearly reassessment in order to evaluate if new risk factors develops. Importantly, this re-evaluation should consider both VTE recurrence risk and bleeding risk to determine the continuous optimal net clinical benefit for the duration of treatment.

High recurrence risk

Much focus has been on identifying patients who can safely stop their anticoagulation after the initial treatment period. However, for many patients, risk of recurrence remains high also after anticoagulation discontinuation [5,25]. In **Study 2**, 90% of the men and 20% of the women were categorized has high risk. The new risk scores in **Study 2** may support the clinical decision to suggest continued treatment for these patients until yearly reassessment discovers a changed clinical picture, e.g., newly discovered increased bleeding risk.

Other VTE prediction models

One of the existing prediction models focused on risk prediction for women only (HER DOO2) as the investigators were unable to identify men with a low recurrence risk (see Table 5 on page 31). In the remaining models [48–50,52,54], male sex was a predictor of higher risk of recurrence. As in **Study 2**, the L-TRRiP study found surgery to be a predictor of lower risk of recurrence [54]. Two models found higher age to be predictive of recurrence [48,52], whereas the DASH model described age < 50 years to be associated with higher recurrence risk [50]. In the L-TRRiP study, age was not selected in the backward selection process. In their development cohort, the mean age was 48 years, while in their validation cohort the mean age was 66 years, which was similar to our mean age in **Study 2**. D-dimer either on or after anticoagulant treatment was included in most models, with the exception of two of the models in the L-TRRiP study [54].

Similarly to the AIM-SHA-RP model, the L-TRRiP study included patients both with 'unprovoked' and 'provoked' VTE [54]. However, their models require extensive laboratory blood testing and may thus be considered impractical for routine clinical care. Whether to aim for a model that is clinically applicable using readily available parameters, or to aim for a perhaps more precise and nuanced model requiring apps or electronic devises for calculation may be partly determined by data available for development – partly by personal preferences. Notwithstanding, prediction models should never rule out good clinical consideration.

VALIDATION OF PREDICTION MODELS

Text box: Relevant definitions when validating prediction models [81,133]

Calibration refers to the agreement between observed outcomes and predictions from the model. Calibration can be visualized on a calibration- or 'validation' plot, or formally investigated using statistical tests.

Discrimination refers to a prediction model's ability to discriminate between those with and those without the outcome of interest. The concordance (C) statistic is the most commonly used performance measure to indicate the discriminative ability. The C-statistic ranges from 0.5 to 1. A value of 0.5 indicates no discriminative ability (like tossing a coin), and values above 0.5 indicate positive discriminative ability, where 1 is perfect discrimination.

Internal validation aims to test if predictions are valid for subjects from the underlying population. Apparent performance refers to validation assessed directly in the sample where it was derived from. Internal validation can be done using various statistical techniques, e.g., bootstrap validation, and split-sample validation.

External validation is referring to the generalizability or transportability of the prediction model to other populations with the same disease. The external validity should be tested in samples fully independent from the development data. Preferably, the external validation should be both temporally, and geographically different, and performed by different authors ensuring fully independent validation.

C-statistic

Validation is an important aspect in the process of predictive modelling. When both presenting and evaluating prediction models, much attention has solely been on the C-statistic. This is, however, a simplistic way of assessing prediction model performance [95]. When making qualified decisions on treatment duration of anticoagulation, an important feature of a model is to be well-calibrated (the predicted recurrence risk corresponds well with the actual observed risk of the patient) while consistently stratifying patients below and above well-defined treatment decision thresholds [95]. In the context of VTE, the central question is whether or not to continue anticoagulant treatment. To answer this, the patient's estimated future absolute risk of recurrence is required. In **Study 2**, the models

were well calibrated (Figure 7) but the discriminative power in terms of C-statistics was low.

An example of a widespread model used in clinical practice despite moderate discriminative power is the CHA_2DS_2-VASc score for atrial fibrillation patients [96]. In development, the model had a C-statistic of 0.601. However, as in VTE, the important key issue is more whether the model allows for stratification below and above a decision threshold more than the discrimination. When using the CHA_2DS_2-VASc score, patients are to be considered for life-long anticoagulation if they reach a certain score threshold (score ≥ 1 for men and score ≥ 2 for women) [97].

Previous recurrent VTE prediction models

Previous recurrent VTE prediction models have been sparsely externally validated [54,83–86] (see Table 8). Some studies did temporal external validation [83,86], others did geographical external validation [54,84,85]. In the external validation of HER DOO2, it is unclear whether the validation was performed using different countries and/or centres, or if there was a geographical overlap with the centres used in the development of the model [83]. The external validation studies were based on 8 recurrent events in the smallest study (DAMOVES) [86], and 123 recurrent events in the largest study (DASH) [84]. In the validation study of the Vienna model [84], the first author of the original developed model was co-authoring the validation study [84]. In the remaining validation studies, same first author of the original developed model was also first author of the external validation study [54,83,85,86]. Hence, none of the models have been, by definition, fully independently validated [81]. The discriminative capacitive ranges from C-statistics of 0.54 to 0.83. In the external validation of HERDOO2, no plots were shown nor was statistical testing performed to assess the calibration of the model [83]. External validation of the DAMOVES model was done in an accompanied publication in a "Letter to the Editor" [86]. Here, calibration performance was reported with a p-value of 0.125 from a Hosmer-Lemeshow test without any plots [86]. In the study by Timp et al., four prediction models were developed with varying complexity [54]. In the development study, they also performed external validation using another cohort. However, external validation could only be done on two out of the four models because laboratory markers for the remaining models were not available in the validation cohort.

Future validation

In **Study 2**, internal validation was assessed through calibration and discrimination using bootstrap techniques [98]. Before used in clinical practice, the developed scores

should be externally validated in other cohorts. Furthermore, future validation studies could, beyond standard external validation procedures, try to add relevant factors (e.g., validated codes for trauma with fracture, relevant biochemical measures such as d-dimer) to the developed scores and evaluate possible optimized performance measures. Importantly, risk estimates for the individual patient should be robust and well-calibrated, both in the derivation study but also in future validation studies.

Table 8: Validation of previous prediction models

	HER DOO2 [83]	**Vienna** [84]	**DASH** [85]	**Damoves** [86]	**L-TRRiP** [54]
External validation	Temporal	Geographical	Geographical	Temporal	Geographical
Patients (with recurrence)	2747 (70)	904 (123)	827 (100)	121 (8)	587 (73)
Discrimination (C-statistic)	÷	0.63	>65 years: 0.54 <65 years: 0.72	0.83	0.64
Calibration	÷	Calibration-plot	Calibration-plot	Hosmer-Lemeshow	Calibration-plot
New first-author	÷	(+)*	÷	÷	÷

*The first author from development of the model was part of the validation.

ADHERENCE

Adherence to a medication regimen is generally defined as the extent to which patients take their prescribed medication [99]. Medication adherence is influenced by numerous factors, including socioeconomic factors, the healthcare team/system, characteristics of the disease, and patient-related factors [99–102]. Furthermore, medication costs and insurance coverage have been described as rather consistent predictors of medication adherence [101,103].

Poor adherence to medication regimens accounts for considerable worsening of disease and death [99]. A Cochrane review from 2002 found that increasing medical adherence may have a far greater impact on the health of the population than any improvement in specific medical treatments [104]. Although the NOAC's offer some advantages, underuse of anticoagulation is still an issue of concern [9]. However, despite adherence being a key factor for successful treatment, no previous studies have investigated patient-related predictors of non-initiation.

For VTE recurrence risk investigated in **Study 1,** we observed a substantial lower number of patients in a sub-analysis restricted to VTE patients initiating anticoagulation within 10 days after discharge, indicating potential underuse. This inspired the development of the third study aiming to investigate possible predictors of not initiating anticoagulation after incident VTE.

STUDY 3

Study 3 was made in cooperation with: Samuel Z. Goldhaber, Gregory Piazza, Thure F. Overvad, Peter B. Nielsen, Torben B. Larsen, and Mette Søgaard [105].

Aim: In **Study 3**, the aim was to investigate incidence of possible predictors for not initiating anticoagulation after incident VTE.

Methods: We linked Danish nationwide health registries to identify all patients with incident VTE who were free from cancer from 2003 through 2016. The cohort entry was set to the earliest time of available socio economic data (year 2003). Patients were defined as 'non-initiators' when not redeeming a prescription for anticoagulation within 30 days after the incident VTE, including heparin, warfarin, phenprocoumon, or a NOAC. Conversely, VTE patients redeeming a prescription in this period were defined as 'treatment initiators'. To identify potential predictors of non-initiation, relative risks with 95% CI were calculated using a log-link function including other covariates associated with adherence. As potential predictors for not initiating treatment, we investigated *(i) demographic factors*, *(ii) socio-economic factors, (iii) major chronic diseases*, *(iv) condition-related factors,* and *(v) concurrent medication use*. To explore if introduction of NOACs affected the proportion of untreated patients, an additional analysis was performed examining the study period before and after year 2012 (corresponding to introduction of the first NOAC drug, rivaroxaban, approved for VTE treatment in Denmark) [57]. We further examined the specific types of anticoagulant drugs used from year 2012-2016.

Results [105]: The final study population comprised 38,044 incident VTE patients. A total of 24.1% (n=9,294) did not initiate anticoagulant treatment within the first 30 days. Most robust predictors of not initiating anticoagulant treatment were demographic and condition-related factors, including: age < 30 years, female sex, incident DVT, 'unprovoked' VTE, and hospitalization < 4 days, whereas socioeconomic factors had less influence on the risk of non-initiation (Figure 8). Heart failure, ischemic heart disease, and liver disease were also predictors for not initiating treatment. Suffering from multiple chronic diseases was not associated with anticoagulant treatment non-initiation. The proportion of patients not initiating anticoagulant treatment remained virtually unchanged when stratifying by calendar period; 2003-2011 (25.2%) and 2012-2016 (23.1%) (Figure 9). Until 2012, warfarin was the primary anticoagulant drug used. Thereafter warfarin was

partly replaced by NOACs, of which rivaroxaban accounted for 23.6% of the total anticoagulant drug use and 86.1% of the total NOAC use (Figure 9) [105].

Conclusion: Up to 24% did not initiate anticoagulant treatment 30 days after discharge with incident VTE. Predictors of non-initiation found were DVT, 'unprovoked' VTE, age < 30 years, hospitalization < 4 days, and female sex [105]. Improving information or treatment follow-up strategies for patients with these specific characteristics may improve treatment adherence [105].

Figure 8: Adjusted relative risk of characteristics associated with not initiating anticoagulation within 30 days of incident VTE [105].

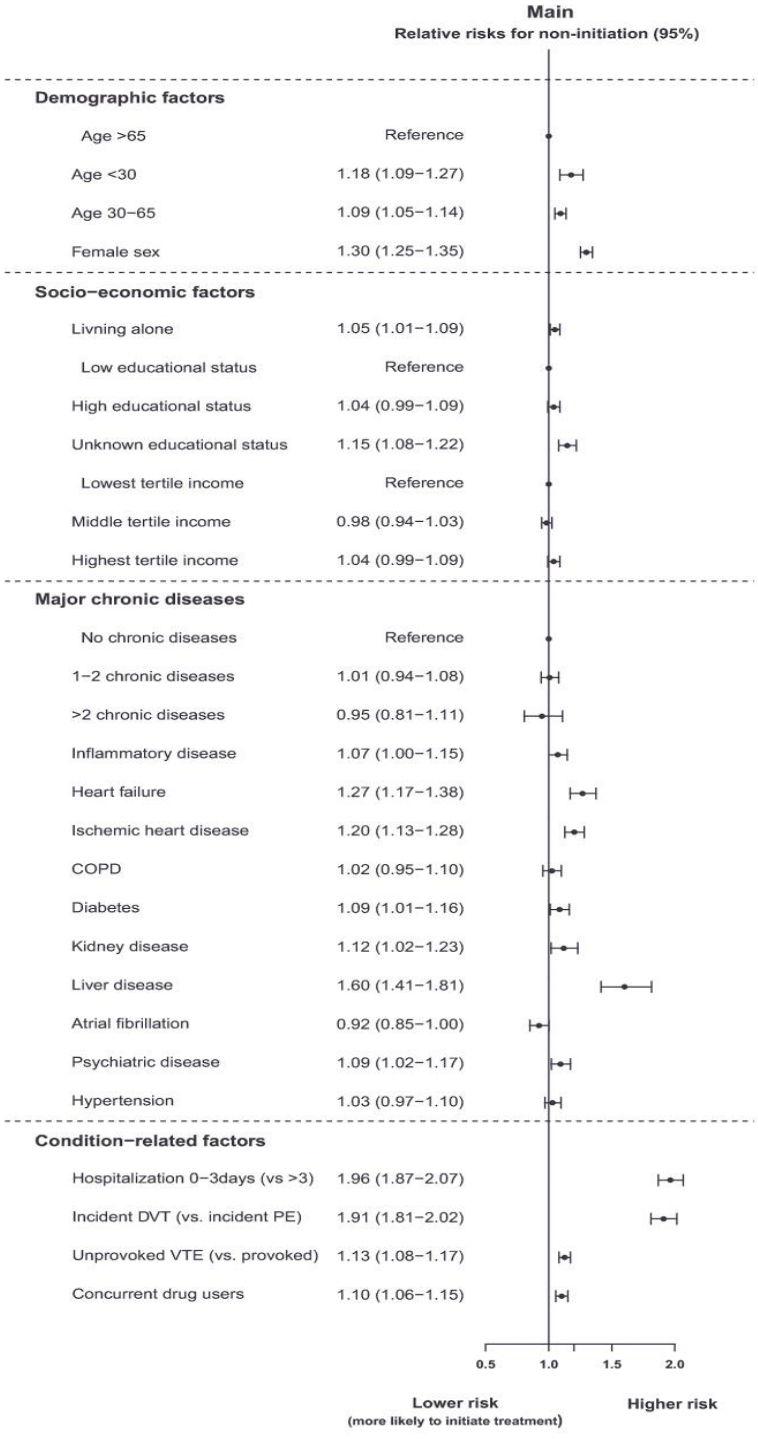
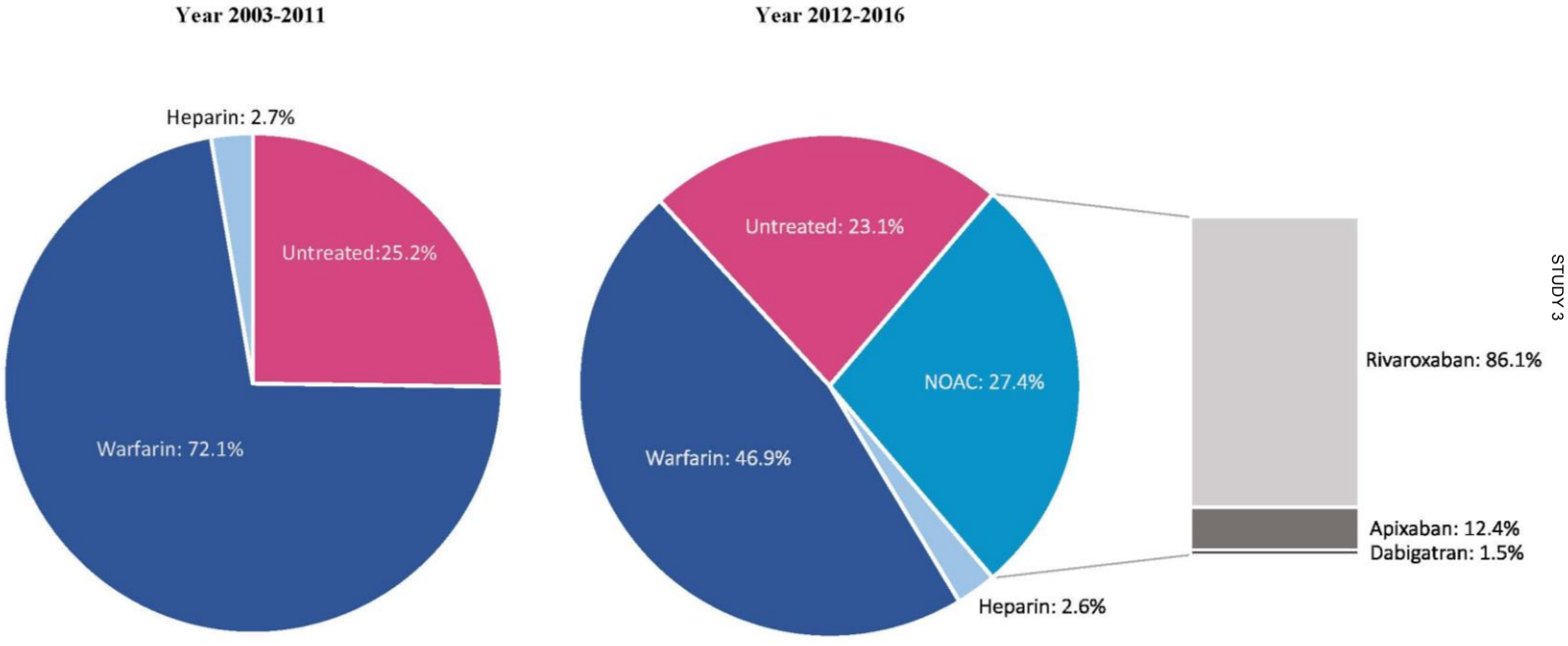


Figure 9: Anticoagulant treatment patterns before and after 2012 [105].



DISCUSSION AND PERSPECTIVES (STUDY 3)

Medication costs tends to affect adherence[101,103]. In our study, however, we did not find socio-economic factors to be predictive of non-initiation. This could be due to the fact that Denmark has a free-of-charge tax-supported health-care system, where all medications are partly reimbursed, possibly making the social gradient less pronounced. However, despite our developed healthcare system, anticoagulant treatment is generally not optimal. In a Danish study comprising 116,051 atrial fibrillation patients, only 63% of outpatients and 42% of inpatients initiated oral anticoagulant treatment 6 months after discharge [106]. Furthermore, in Danish studies of atrial fibrillation patients with a life-long treatment indication, the proportion of anticoagulation discontinuation ranges from 26% to 38% after 3 years [57,107]. Similarly, a Canadian study reported that 26% of 40,776 VTE patients not were dispensed with anticoagulation following a VTE diagnosis [108]. In an American study of treatment patterns and outcomes among hospitalized patients with VTE, a non-initiation proportion of 40% was found [109].

The association of sex and adherence has previously been described as either neutral or with females being less compliant [101,103]. In our study, we found female sex to be a predictor for not initiating treatment. In a Dutch study on NOAC persistence in patients with atrial fibrillation, female sex, and no concomitant drug use were predictors for non-persistence [110]. Of note, in our study, we cannot exclude the possibillity that the PPV of the incident VTE diagnosis may differ for example between men and women, potentially explaining the observed sex-specific association towards non-initiation.

In our study, patients with DVT were more likely to be non-initiators than patients with PE. A recent American study confirmed an association of VTE-type and anticoagulant treament: 94% of patients with PE were discharged with anticoagulation compared to 87% of patients with lower extremity thrombosis [111]. However, discharging with treatment is not necessarily equivalent to patients continuing treatment or even initiating treatment after their hospital-managed medicine during admission. Hence, the proportion of patients acutally on treatment might be lower 30 days after discharge. A Dutch study described a 2-month cumulative incidence of completely stopping NOAC of 20% for patients with an acute VTE[112]. The study only looked at patients initiating treatment, while patients never initiating treatment was not invetigated.

Medical adherence is typically higher in patients with acute conditions as opposed to patients with chronic diseases, especially when treated with simple dosing [99,103]. Nonetheless, we found that almost 1 in 4 did not initiate anticoagulant treatment for incident VTE, even after introduction of the NOACs. No obvious explanation exists for the relatively high proportion of untreated patients. However, this could indicate that medication adherence is a multifaceted challenge with no easy solutions. We probably should seek solutions at both at the individual level and the system level.

IMPROVING ADHERENCE

Some research on optimizing medication adherence exists. A meta-analysis from 2016 found that mobile phone text messaging approximately doubled the odds of medication adherence in patients with chronic diseases [113]. A Swedish study investigated the effect of a telephone call one week after a cardiovascular prescription filled at the general practitioner. In total, 95% (n=174) of the patients receiving a phone call filled their prescriptions, as opposed to 87% (n=188) in the control group. The analysis showed that primarily women were affected by the telephone call [114]. For patients treated with rivaroxaban or apixaban for acute VTE, a phone call could be at the critical point when shifting from high to reduced dose medication [115]. From an academic perspective, one attempt to reduce the proportion of non-initiators could be a formally developed risk stratification model using patient characteristics to determine future risk of non-initiation.

In Denmark, it is recommended that possible extended anticoagulant treatment of VTE patients is evaluated at a follow-up visit after the initial 3-6 months treatment [19]. This recommendation is, however, implemented differently across hospitals. Some patients are followed-up by cardiologists, others by internal medicine departments, some by a general practitioner, and some are likely not followed-up at all. Presumably, adherence could benefit from a more uniform follow-up structure.

A vital responsibility lies with the clinicians treating and diagnosing VTE patients. More focus is necessary on patient education, emphasizing the nature and severity of the disease. Improved communication between physician and patient, and more frequent follow-up visits could also be areas to work with. Before more knowledge and research is available on how to best improve adherence, easily available

predictors from our study could be used to flag up patients with a high risk of being left untreated after hospital discharge. Improving information or treatment approaches for patients with these specific characteristics may improve treatment patterns.

METHODOLOGICAL CONSIDERATIONS

All three studies forming the basis for this thesis used information from national Danish registries. A brief description of the relevant registries can be found in the Text box below (also described in the studies[5,93,105]). The Education Registers and Income Statistics Registries were only used in **Study 3**. As in all observational studies, systematic errors may affect the validity of our findings. We must therefore critically evaluate alternatives to causal interpretation when evaluating our findings.

THE DANISH REGISTRIES

Text box: Administrative nationwide registries used in study 1-3

The Danish Civil Registration system [87] established in 1968 holding information on sex, date of birth, vital and emigration status on all Danish residents. In Denmark, all residents are assigned a unique national identification number (Central Person Register/CPR-number) at birth or upon immigration allowing for individual-level linkage of data from all national registries.

The National Patient Register [134] established in 1977, which includes dates of admission and discharge diagnoses classified according to the *International Classification of Diseases* (ICD) for more than 99% of hospital admissions in Denmark. In Denmark, ICD-8 was used from 1977 through 1993 and ICD-10 from 1994 and onwards. Since 1995, information from emergency room contacts, and hospital outpatient clinics has also been recorded.

The Danish National Prescription Registry [123], containing individual-level information on purchase date, Anatomical Therapeutic Chemical (ATC) classification codes, and dose units for all prescriptions claimed since 1994.

The Danish Education Registers [135] holding information on highest completed education for 96% of the Danish population aged 15–69.

The Danish Income Statistics Registry [136] holding information on personal income and transfer payments dating back to 1970. Among other, the register contains information on average gross income (income subject to ordinary taxation - calculated by Statistics Denmark), and taxable income.

STRENGTHS AND LIMITATIONS OF THE DANISH REGISTRIES

Danish registries are well-known for their nationwide coverage with complete follow-up in epidemiological terms basically making Denmark an "entire cohort" [116]. Population-based cohort studies is a specific category of epidemiology studies where a defined population is followed up and observed longitudinally to assess exposure and outcome relationships [117]. Observational cohort studies are designed with the capacity to address a wide range of research topics that can be generalized to a community or an even broader population than e.g. a cohort enrolled in a randomized controlled trials can [117].

The Danish registries offer great advantages and strengths. In general, the number of patients is large minimizing the risk of *random variation* meaning that the results are less likely to be due to chance. The registers are well-established, offer almost full follow-up and include a large amount of health-related information, which, when used wisely, may help close knowledge gaps or identify options for treatment optimization. However, even though the well-developed registries are a tremendous resource in research, they also come with some limitations.

Register-based research is dependent on complete and valid coding of diseases. Inherited thrombophilias is an example of diseases with expected incomplete coding. It is estimated that 25% of VTE patients have a Factor V Leiden mutation, and 3% suffer from Protein C deficiency [118]. However, in **Study 2** only 0.4% had a thrombophilia code (among other covering both Factor V Leiden heterozygote and –hemizygote, prothrombin mutations, protein C and S deficiencies, and antiphospholipid antibody syndrome). Despite low completeness, the PPV may still be high. In epidemiological terms, this means that the sensitivity of an administrative diagnostic code for identifying thrombophilia is low.

Another challenge is when potentially relevant diseases or conditions do not have a code in the registries. In the field of VTE, it could be relevant with separate codes for proximal/distal DVT, codes for long haul flights, and codes for family history of VTE, but none of these conditions have an ICD-code. In some situations, this can partly be solved by using proxies, e.g. using chronic obstructive pulmonary disease as a proxy for smoking. This is, however, more unspecific and the accuracy of the proxy is dependent on the strength of the association between the measured proxy and the condition of interest.

INFORMATION ISSUES – VTE DIAGNOSES IN THE REGISTRIES

Despite the use of well-established registries, internal validity of observational studies can still be threatened by bias. In epidemiological studies, erroneous information collected about the study subjects may result in misclassification of the exposure or the outcome (*information bias*) [119]. The PPV of both incident and recurrent VTE diagnoses in Danish registries have been validated [120–122]. Generally, the PPV of VTE diagnoses are low when coded in emergency wards (31%) [122]. These codes are not included in any of the studies in this thesis. The PPV of VTE diagnoses coded in wards, on the other hand, are higher [121].

Incident VTE: Highest PPV for VTE codes is found when limiting to diagnoses coded in combination with a relevant imaging examination (e.g. CT-scan or ultrasound), as done in **Study 1 and 3** (see Table 9). For incident VTE, this ensures a PPV of 91% [121]. Consequently, of the patients included with a presumed incident VTE, 9% may be misclassified and never had the event. These patients will have a lower risk of recurrence (compared to patients with previous VTE) and lower the total estimated recurrence risk (**Study 1**), or they will rightly not initiate anticoagulation (**Study 3**) since they never have had a VTE. Validity of incident VTE diagnoses can also be ensured by restricting to VTE patients initiating anticoagulation within 30 days after discharge, as done in **Study 2**. This approach ensures a PPV of 90% for incident VTE diagnoses [120]. This approach was not possible in **Study 3** where the 30 days after discharge were used to classify the patients as initiators or non-initiators. Instead, in **Study 3**, we only included primary codes likely increasing the PPV [121]. Of note, in the validation study when deriving at the PPV of 91% both primary and secondary codes were used [121].

In **Study 1**, the exposure of interest was the incident VTE-type. The definition of 'provoked' VTE was based on a review of international guidelines and relevant literature, in combination with available codes in the registries. More diseases/conditions could have been relevant to include in a 'provoked' VTE definition had they had an ICD-code. Consequently, there is a risk of misclassification of patients with 'provoked' VTE as 'unprovoked' patients. This misclassification is, however, most likely not related to the outcome making it non-differential. In **Study 1**, we also defined a group consisting of patients with 'unprovoked' VTE for whom the risk of occult cancer was not taken into account.

Recurrent VTE: Some recurrent VTE diagnoses in the registries may reflect subsequent examinations related to the incident VTE event rather than actual recurrent VTE. Clinically, it may be difficult to determine whether the finding of a DVT at a 3-month follow-up visit represent recurrent event or not. For recurrent VTE, a relevant imaging examination in association with a diagnosis ensures a PPV of 82%. This definition was used in both **Study 1 and 2** (Table 9). Accordingly, 18% may be misclassified and falsely coded as suffering recurrence. These patients will, as opposed to the patients with a false incident VTE diagnosis, lead to an overestimate of the recurrence rate. The PPV of recurrent VTE is not validated for specific sub-types of patients, e.g. patients with cancer, patients with 'unprovoked' VTE, and patients with specific co-morbidities. However, the misclassification of recurrence is most likely not related to the exposure making it non-differential in relation to our exposure groups. In **Study 1**, we minimized the risk of repeated coding (inclusion of falsely coded recurrent events) further by starting follow-up 10 days after discharge from the hospital. In both **Study 1 and 2**, the recurrent diagnoses were restricted to primary codes which we expect will increase the PPV further, although this was not specifically investigated in the validation study [121]. Conversely, some factors contribute to underestimation as previously mentioned; not including emergency ward diagnoses, and fatal VTE's never registered as VTE events. Hence, the 'true' magnitude of VTE recurrence is therefore impossible to perfectly estimate using administrative registries.

In **Study 3**, the outcome was not redeeming a prescription within 30 days of discharge. This information was based on data from The Danish National Prescription Registry [123], containing individual-level information for all prescriptions claimed since 1994. The PPV of this outcome was therefore 100% with no misclassification issues.

Table 9: Diagnoses and Positive Predictive Values (PPV's) by varying definitions

	Study 1	Study 2	Study 3
Study population	Incident VTE	Incident VTE	Incident VTE
Study population requirements	Imaging examination: PPV 91%.	Initiating anticoagulation: PPV 90%.	Imaging examination: PPV 91% + primary diagnosis.
Outcome	Recurrent VTE.	Recurrent VTE.	Not initiating anticoagulation.
Outcome requirements	Imaging examination: PPV 82% + primary diagnosis.	Imaging examination: PPV 82% + primary diagnosis.	Not redeeming a prescription within 30 days of discharge: PPV 100%.

SELECTION ISSUES

Another type of bias is *selection bias*. Selection bias can be introduced both at the time of study conception or during the study process [119]. In the design phase of a study, selection bias can occur if there is a systematic difference between exposure and outcome in those included in the study compared with those not included, but otherwise eligible for the study. However, especially in register-based cohort studies, selection at entry into the cohorts is rarely associated with the outcome, since the outcome has not, or at least should not have, occurred at the time of enrolment. During the analytic phase of a study, selection bias can arise from censoring due to differential loss to follow-up or competing risk (informative censoring) [124]. However, as the registers offer almost complete follow-up, the potential selection bias arising from informative censoring due to loss to follow-up was negligible.

DEATH AS COMPETING RISK OR RECURRENT VTE

As mentioned, selection bias can occur as a result of competing risk. A competing event is something that precludes or fundamentally alter the probability of the occurrence of the event of interest [90]. When trying to determine the risk of

recurrent VTE, death can be thought of as a competing event. Translated to VTE research, this means that when a patient suffers a VTE and dies 5 months after the clinical event, estimating the risk of recurrence for this patient 2 years after incident VTE is not feasible. If mortality risk varies in sub-groups of a study, this might constitute a problem when using time-to-event analysis, where the assumption of non-informative censoring must not be violated. Focus on competing risk has recently emerged and few studies take this into account when considering VTE recurrence risk [33,39,125]. However, when dealing with a potentially fatal outcome such as recurrent VTE, it may not be reasonable to categorise all deaths as competing events, since some fatal VTE events are likely to not have been coded as such.

Another possibility is that death after incident VTE is a recurrent fatal VTE event. In that case the patient should not be censored in a time-to-event analysis but instead registered as suffering the outcome of recurrent VTE. Death associated with recurrent VTE was examined in a review from 2018 on 6,758 patients with a first 'unprovoked' VTE. The authors found the rate of fatal recurrent VTE was 0.17 (95% CI 0.05–0.33) per 100 py one year after anticoagulation cessation [126]. The review included 18 studies with varying definitions of fatal recurrent VTE. In a dated Danish study from 1989 investigating the presence of PE in autopsy material from a general population, 210 patients (13%) of a total of 1.603 patients had PE at autopsy. Of the 74 cases with lethal PE, two thirds were not recognized with PE prior to autopsy. The study concluded that the vital statistics of the Danish Board of Health underestimate the true number of cases and that PE should be considered in the differential diagnosis more frequently [127]. The same conclusion was reached in a study from 1995: a PE diagnosis was unsuspected in 14 of 20 (70.0%; 95% CI 45.7;88.1) patients who in autopsy were found to die from PE [128]. This could argue that the risk of dying from recurrent VTE is in fact higher than estimated in studies not using autopsy data.

In **Study 1 and 2**, we used time-to-event analysis treating death as a censoring event (not a recurrent VTE). In both studies, however, we used the Aalen-Johansen estimator, assuming death as competing risk, to depict the cumulative absolute recurrence risk. Furthermore, in **Study 2**, we did a supplementary analysis investigating the performance of the risk scores when predicting risk of recurrent VTE and death as a combined outcome. Using these analytic approaches, we investigated the performance of the models when all deaths were considered potential recurrent events instead of a competing event. In **Study 3**, patients dying

within the 30 days of discharge without redeeming a prescription were excluded. If anything, this exclusion will then lead to a possible underestimation of the proportion of non-initiators as defined by the 30-day mark since the group excluded were all non-initiators.

GENERALISABILITY

Generalisability or external validity is the degree to which the results of scientific findings hold true in other populations than the study population itself [119]. As debated under "Validation of prediction models", the predictors found in **Study 2** should be externally validated in other cohorts, before used in clinical practice. Furthermore, the results of **Study 2** are based on VTE patients initiating and discontinuing anticoagulation within 1.5 years. In **Study 3**, the results were found after excluding non-initiators dying within 30 days after discharge. Finally, risk of recurrence investigated in **Study 1**, was based on patients hospitalized in Denmark with a VTE. These apparent choices does not mean that the results are biased but should instead be considered when evaluating for whom the results are valid and relevant for.

EFFECT MODIFICATION BY ANTICOAGULATION

When investigating recurrent VTE the risk estimates are likely to be modified by anticoagulation treatment. Effect modification occurs when the strength of the relationship between the primary exposure (incident VTE) and the outcome (recurrent VTE) differs depending on the level of a third variable (anticoagulation) [119]. Hence, anticoagulation may be considered an effect modifier by significantly lowering recurrence risk and death in patients with VTE [129].

Unselected cohorts of patients with VTE not treated with anticoagulation no longer exist. Consequently, the natural history between incident VTE and recurrent VTE can no longer be studied using contemporary data, and researchers investigating recurrence risk are required to choose between different approaches. One option is to define a cohort using only patients not treated with anticoagulant agents, and subsequently censor patients once they initiate antithrombotic treatment. Importantly, this approach lacks of knowledge about why these particular patients were left untreated. This may impact on the generalizability of the results. Another

option is to include all patients with VTE irrespective of anticoagulant treatment status during follow-up, and describe an association recognizing that treatment status may vary. In Denmark, most cancer-free patients are treated for a time-limited period of 3-6 months after incident VTE [19]. Assuming that the treatment-status primarily varies during the first year, in **Study 1**, the main analysis included all incident VTE patients. However, because of a continued indication for anticoagulation, we excluded patients with atrial fibrillation and patients with pre-existing oral anticoagulant use within the last year. Furthermore, we conducted a supplementary analysis, repeating the main analysis with restriction of the study population to patients who had claimed a prescription for oral anticoagulation within 10 days of discharge from the index event. Results of the supplementary analysis restricted to patients on OAC treatment did not differ from results of the main analysis.

In **Study 2**, we aimed to describe recurrence risk for an untreated population. The study population was followed from discontinuation of anticoagulation based on information from the Danish National Prescription Registry, [123]. After start follow-up, patients were censored if they resumed anticoagulation. Hence, we expect no effect modification by anticoagulation in this study. In **Study 3,** we used the same registry to identify patients initiating treatment within 30 days after discharge as opposed to non-initiators not redeeming a prescription within this period. Anticoagulation was therefore not an effect modifier in that study, rather it was used to define the outcome (to not initiate anticoagulation). Since the prescription registry holds information on all claimed prescription drugs, the PPV of this outcome can be classified as 100%. That said, dispensing a prescription for a drug at the pharmacy is not equivalent to actually taking the drug as prescribed.

CAUSALITY VERSUS PREDICTION

Importantly, descriptive studies or studies of prediction should not be mistaken for aetiological studies [130]. Aetiology aims at clarifying a causal effect of a specific exposure on an outcome. In non-randomised studies, this requires control for confounding factors selected based on pre-existing knowledge of causal relations [131]. Confounding as a concept is therefore a type of bias specific to studies on causality. In contrast, prediction aims at accurately predicting the risk of an outcome using multiple predictors collectively, regardless of whether the predictors have a causal relationship with the outcome [130].

In **Study 2,** our aim was to predict risk of recurrent VTE. The developed models are based on statistical associations that are not necessarily causal associations between the specific risk component and outcome. Although tempting, the AIM-SHA-RP-variables cannot be interpreted with a causal meaning, e.g., that statin users carry a lower risk of VTE recurrence cannot be interpreted as statins per se *prevent* recurrent VTE – rather, statin use is an easily obtainable predictor or marker of lower risk of recurrent VTE. Furthermore, in **Study 2** chronic renal disease was associated with a lower risk of recurrence. By intuition, a clinician will probably struggle to see the logic in that result. However, based on our study, the underlying reason for these associations cannot be understood. Some of the included components might be known as causes of (recurrent) VTE, but they are included in the models because they serve as easy obtainable patient characteristics that provide useful prognostic information in patients with VTE -not because they are known to cause VTE.

In **Study 1**, we described the risk of recurrence according to incident VTE type, and in **Study 3** we searched to clarify potential predictors of not initiating anticoagulation. None of these were studies of causality and confounding was therefore by definition not a specific concern [132]. That said, whether specific information not available in the registries, e.g. lifestyle, would improve the prediction of anticoagulant non-initiation, remains unknown.

CONCLUSIONS AND PERSPECTIVES

Anticoagulant VTE treatment is filled with dilemmas. Several issues require considerations before we can determine the optimal anticoagulant treatment for the many patients suffering from VTE.

Risk of recurrence and bleeding
Ideally, VTE risk stratification should help the decision of anticoagulant treatment duration by estimating a recurrence risk and identifying low or high-risk subgroups who should stop or continue treatment, respectively. **Study 1** investigated the dilemma of recurrence risk according to the stratification used in most guidelines, namely: 'provoked'/'unprovoked'/'cancer-related' VTE. This was undertaken knowing that the concept 'provoked VTE' is not consistently defined making a unanimous categorization challenging. Recurrence was generally frequent affecting 15-20% of all incident VTE patients after 10 years of follow-up. Patients with 'cancer-related' VTE had the highest recurrence risk followed by patients with 'unprovoked' VTE. However, an overall high recurrence risk in all types of VTE – also after 'provoked' VTE – underscored that refinement is needed to optimize risk stratification for VTE patients.

In **Study 2,** two new risk prediction scores under the joint acronym AIM-SHA-RP for men and women were developed. The models were designed to disregard the historical distinction of 'unprovoked' and 'provoked' incident VTE. After further external validation, these new risk scores may prove as useful shared decision-making tools to guide the dilemma of duration of anticoagulation after incident VTE in everyday clinical practice.

The risk of recurrence and consequent treatment duration should be balanced against an associated risk of bleeding while anticoagulated. For decades, VKA has been the only treatment option after VTE, but is now partly replaced by the NOACs. However, uncertainty remains in estimates of the long-term risk of major bleeding if treatment is continued. Furthermore, limited data exist on which is the safest and most effective NOAC due to lack of head-to-head trials comparing the NOACs [58,63]. The newly developed reversal agents for the NOACs may support the paradigm shift towards extended treatment duration.

Adherence and patient preference

Despite of the NOACs offering practical advances for the patient compared to VKA, many patients with VTE never initiate relevant anticoagulant treatment. **Study 3** identified that up to 24% did not initiate anticoagulant treatment 30 days after discharge with an incident VTE event. Improving information or treatment follow-up strategies for patients with specific characteristics may improve treatment patterns. However, the many facets of medication adherence precludes an easy accessible strategy for treatment optimization. Future targeted optimized adherence interventions have to consider both a clinical and academic perspective to reach the goal of improved treatment for patients suffering a VTE. However, facilitating this requires patient-tailored interventions and health professionals need to better understand adherence, besides offering anticoagulation to appropriate patients. Whether the effort should focus on generally reducing the total proportion of untreated, or if actions should be targeted few specific patients, with high risk of not being treated, remains undetermined.

Register-based VTE research

The Danish national healthcare system provides a unique setting for conducting large population-based studies of VTE. The civil registration number makes it possible to link medical databases and administrative registries, and thereby construct large cohorts with detailed longitudinal data that include comorbidity data from hospital contact history, and complete long-term follow-up data. Our studies have, however, also encountered some of the weaknesses in the Danish health care databases. The coding of VTE diagnoses is not rigorous as seen in, especially, moderate PPV for VTE recurrence codes. Also, there is a lack of relevant VTE codes in the registries including distal/proximal position of a DVT. An ideal future prediction model for VTE recurrence could be using big data and machine learning techniques implementing both electronic medical records, socio-economic data, geographic factors and allow for a much more detailed characterization of patients and thereby precise risk estimate of both recurrence and bleeding risk.

In conclusion, this Ph.D. dissertation emphasizes that there is a continued need for improvement of VTE treatment and management. It clarifies that VTE recurrence is common after all types of VTE, and that many patients receive no or potentially sub-optimal anticoagulant treatment. The concept of VTE is undergoing a major transition in the scientific and clinical community as we increasingly consider VTE as a chronic illness. The presented studies may help navigate some of the VTE

dilemmas and together with other scientific contributions support the decision of anticoagulant treatment duration of the many patients with VTE.

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APPENDICES

Appendix A. Paper 1

Appendix B. Paper 2

Appendix C. Paper 3

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